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ORIGINAL PAPER

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Diagnostic confirmation, severity, and subtypes of Alzheimer's disease

A short review on clinico-pathological correlations

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Introduction

The title of this paper is open to four different interpretations: (a) "clinico-pathological correlation" as the verification (or falsification) of a clinical diagnosis of "probable" or "possible" Alzheimer's diseases (AD) by the pathological examination of brain tissue; (b) the verification (or falsification) of a neuropathological diagnosis of AD by clinico-neuropsychological measures; (c) the statistical correlation between the severity of clinical and neuropsychological data with the severity of various neuropathological changes; and (d) the distinction of different subtypes of AD with characteristic clinical and corresponding neuropathological features. These topics have already been addressed by A. Alzheimer, who described clinical and histopathological features distinguishing senile dementia from vascular dementia (1895, 1898) and discussed quantitative differences among various forms of degenerative dementia (1907, 1911). In 1911, T. Simchowicz, a coworker of A. Alzheimer, was the first to define the borderland between senile dementia and "normal" brain aging and to suggest a quantitative cut-off value of ten senile plaques per visual field (i.e. 1.77 mm^2) (Simchowicz 1911; Fischer et al. 1991). In spite of their long histories, none of these issues has lost its importance.

Neuropathological verification of Alzheimer's disease

Reliable intravital diagnostic markers of AD are not currently available, even though numerous studies have reported significant differences between AD and other dementias or non-demented control groups regarding neuroradiological, neurophysiological, and neurochemical findings (Förstl et al. 1993). The clinical diagnosis of AD has been summarized and operationalized by the NINCDS-ADRDA work group (McKhann et al. 1984). Neuropsychological deficits should be documented in two or more areas of cognition and should usually include a progressive worsening of memory. Other brain diseases or systemic disorders that "in and of themselves" could acount for the progressive deficits in memory and cognition have to be absent for a clinical diagnosis of "probable" AD. The "definite" diagnosis of AD can only be verified by histopathological evidence obtained with a brain biopsy or at autopsy after a dementia syndrome has been established by clinical examination (McKhann et al. 1984).

Clinicians tend to ignore the fact that standardized neuropathological criteria for the "verification" of AD are also based on the exclusion of other obvious causes of organic dementia, such as chronic subdural haematoma, neoplasm, "Pick's disease", or cerebral infarcts (Khachaturian 1985). Criteria which have to be fulfilled for the diagnostic verification of AD according to the National Institute of Aging are given in Table 1. Plaque and tangle density in the cortex of non-demented individuals in-

Table 1 "National Institute on Aging" (NIA) criteria for the neuropathological verification of Alzheimer's disease giving minimum plaque and neurofibrillary tangle counts in different age groups (modified after Khachaturian 1985)

Age (years)	Clinical history	Plaques[a]	Tangles[a]
<50	–	>2–5	–
≤50	[b]	>8	'some'
≤66	[b]	>10	'some'
≥76	[b]	>15	–

[a] Counts per eye field (magnification × 200)
[b] "In the presence of a positive clinical history of AD these criteria should be revised downwards, although to what extent remains to be determined by further research"

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Table 2 The "Consortium to Establish a Registry for Alzheimer's Disease" (CERAD) criteria for the clinico-pathological diagnosis of Alzheimer's disease (for details see Mirra et el. 1991; Mirra et al. 1993)

Diagnosis[a]	Clinical history of dementia	Plaques	Other disease
Normal a	0	0	0
Normal b	0	sparse	–
Normal c	yes	0	0
Possible a	yes	sparse	yes
Possible b	0	moderate/ frequent	–
Probable	yes	moderate	0/yes
Definite	yes	frequent	0/yes

[a] This terminology has to be distinguished from the categories suggested by McKhann et al. (1984)

Table 3 Accuracy of clinical diagnosis of Alzheimer's disease using NINCDS-ADRDA criteria: selected autopsy studies

Reference	*n*	[a]	N'path criteria	Verification (%)
Morris et al. 1987; 1988	26	p	specified	100%
Tierney et al. 1988	22	p	specified	81–88%
Boller et al. 1989	54	r	?	85–95%
Burns et al. 1990	50	p	specified	78–88%
Risse et al. 1990	25	p	NIA	68%
Fischer et al. 1991	44	p	NIA	80%
Mirra et al. 1991	25	p	CERAD	84%

[a] p = prospective; r = retrospective

creases with higher age, and the diagnostic thresholds of plaque and tangle counts are therefore age-related. The arbitrary nature of the cut-off values suggested in Table 1 is underlined by their dependence on clinical history. Using modified NIA criteria, the clinical diagnosis was verified in 56 of 66 patients (85%) with "probable" or "possible" AD who had been examined in a prospective study carried out at the Institute of Psychiatry (IoP), London (Burns et al. 1990; Förstl et al. 1993 a, b). Two of the other patients had Lewy bodies in the cortex and brainstem together with low plaque and neurofibrillary tangle counts, two had mixed Alzheimer-type and vascular brain changes, and two had vascular dementia. No neuropathological diagnosis was found in four patients ("dementia lacking distinctive histological features").

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) has proposed new standards for normal findings of "possible", "probable" and "definite" AD that are also based on clinical and histopathological features (Mirra et al. 1991; Mirra et al. 1993). There are three major modifications in the CERAD standards compared with the older NIA criteria (Tables 1 and 2):

- A diagnosis of "definite" AD can be made in the presence of another disease, for example cerebrovascular disease. This view is compatible with recent standards for the diagnosis of vascular dementia (Roman et al. 1993) and it is in line with the clinical observation of demented patients satisfying NINCDS-ADRDA-criteria for "probable" AD also developing vascular changes later in the course of illness.
- The neuropathological confirmation is based exclusively on cortical plaque counts and not on tangle counts. It is well known that a certain percentage of demented patients has low neurofibrillary tangle density (Terry et al. 1987).
- It is suggested that the diagnosis of "possible" AD can be made purely on neuropathological grounds, even if the patient was not clinically demented. This approach may have advantages for the investigation of very early or "subclinical" forms of AD, but it is in conflict with previous concepts regarding the priority of clinical findings. This approach implies the assumption that the relevant disease process is reflected by the amount of cerebral β-amyloid and thus presupposes that AD is a disease of amyloid metabolism. This hypothesis is still a matter of debate (see below).

Experienced and well-trained examiners can achieve reasonable interrater agreement for the clinical diagnosis of AD if standardized criteria are used (Kukull et al. 1990; McGonigal et al. 1992). The interrater reliability of a neuropathological diagnosis may benefit from the introduction of standardized quantitative criteria, including a standardization of the counting procedure (Duyckaerts et al. 1990), standard staining techniques (Chui et al. 1993), and a discussion of these standard criteria among the neuropathologists involved (Paulus et al. 1992). In spite of several method-related sources of variance, most of the clinico-pathological studies found that the clinical diagnosis of AD was correct in 80–90% of cases (Table 3), a level of accuracy only slightly higher than that reported 70 years ago (Uyematsu 1923). These high success rates may simply reflect the high prevalence of AD and the timely elimination of patients with "difficult" diagnosis in the earliest phase of such studies. These effects have also been relevant in biopsy studies in which very high or perfect agreement between clinical and pathological diagnosis is indicated (DeKosky and Scheff 1990; DeKosky et al. 1993; Martin et al. 1987), while other diseases were found only in atypical cases of dementia (Hulette et al. 1992).

Clinical falsification of neuropathologically "diagnosed" AD

Most clinicians regard neuropathology as the gold standard of AD diagnosis and this is reflected by the term "definite" AD in the NINCDS-ADRDA criteria (McKhann et al. 1984). However, the neuropathologist who investigates the number of plaques and tangles and their regional distribution in an individual brain cannot give a reliable estimate of the patient's previous cognitive performance.

Table 4 Alzheimer plaques (Pl), neurofibrillary tangles (NF), neuron numbers, and their correlation with sociodemographic variables, diagnosis, dementia severity, and cognitive deficits in Alzheimer's disease – a summary of selected postmortem and biopsy studies

Authors	*n*	♂ : ♀	Age (mean ± SD) range; years)	Pro-/ retro-spective; controlled	Neuropathological variables	Clinical correlates	
						Sociodemographic covariates	Neuropathologic change is associated with...
Arriagada et al. (1992)	10	1,4 : 0,6	71 (52–82)	p; C	Pl, NF (fx, px, tx, ox, hippocampus, subiculum, entorhinal cortex, subcortical nuclei)		Severity of illness (with NF, but not with Pl)
Ball (1977; 1978)	8	0,8 :1,2	75 (56–91)	r; C	Neurons, NF (hippocampus)	Less severe neuronal loss with higher age	A diagnosis of AD
Berg et al. (1993)	42	?	> 80	p; C	Pl, NF (fx, px, tx; hippocampus, subiculum, entorhinal cortex)		AD; dementia scale (with NF, but not with Pl)
Blessed et al. (1968)	26	?	79 ± 8	p; C	Pl (fx, px, tx)		AD; dementia score; cognitive performance
Bowen et al. (1979)	17	?	81 (71–89)	?; C	NF, neurons (tx)	Less severe changes with higher age	AD
Crystal et al. (1989)	22	0,7 :1,3	78	p; 0	Pl, NF (fx)		Severity of illness (NF)
Dayan (1970)	40	0,8 : 1,2	> 60	r; C	Pl, NF (fx, hippocampus)		AD (higher NF numbers)
Delaere et al. (1991)	26	0,0 : 2,0	> 75	p; C	ßA4-Pl (tx)		Blessed score (ßA4); depending on the staining technique
Doebler et al. (1987)	11	2,0 : 0,0	74 (59–88)	r; C	NF, neurons (hippocampus, subicullum)		AD
Duyckaerts et al. (1988)	14	0,0 : 2,0	> 75	p; C	Pl, NF (tx)		Blessed score (Pl; NF)
Fuld et al. (1981)	13	?	?	p; C	Pl (fx, tx, px)		Attentional deficits * Pl
Hansen et al. (1988)	113	?	(50–100)	r; C	Pl, NF, neurons (fx, px, tx)	Less severe changes with higher age	
Hubbard et al. (1990)	5	?	(60–95)	p; 0	NF, neurons (subiculum)	Higher NF number with higher age and in females	AD (neurons) AD, Reisberg Scale (NF)
Jamada and Mehraein (1968)	48	0,6 : 1,4	71 (41–92)	r; 0	Pl, NF (fx, px, tx)	Lower Pl and NF numbers with higher age	No correlation with the severity of illness
McKee et al. (1991)	34	?	78 (59–93)	p; C	Pl, NF (fx, px, tx, hippocampus)		AD (Pl, NF) Blessed score (Pl, NF)
Mölsä et al. (1987)	34	0,1 : 1,9	80 (69–88)	p; C	Pl, NF (fx, tx, hippocampus)		AD
Morris et al. (1991)	10	1,3 : 0,7	77 (71–82)	p; 0	Pl, NF (fx, tx, hippocampus)		AD; higher NF and Pl number with advanced dementia
Mountjoy et al. (1983)	25	0,5 : 1,5	81 ± 9	p; C	Neurons (fx, px, tx, ox)		AD (fx, tx)
Samuel et al. (1991)	16	0,6 : 1,4	81 (70–89)	p; 0	NF (fx, ox, subiculum, basal nucleus of Meynert)	Higher NF numbers with longer duration of illness	Inverse correlation between cognition and NF, most significant in the basal nucleus of Meynert: (positive correlation between cognition and NF in area 17!)

Table 4 Continued

Authors	*n*	♂ : ♀	Age (mean ± SD) range; years)	Pro-/ retro-spective; controlled	Neuropathological variables	Clinical correlates	
						Sociodemographic covariates	Neuropathologic change is associated with...
Terry et al. (1981)	18	0,4 : 1,6	81 (70–89)	r, C	Pl, NF, neurons (fx, tx)	Decrease of large neutrons with higher age	Decrease of large neurons in lamina III with AD (fx, tx)
Terry et al. (1987)	60	?	> 74	r; 0	Pl, NF (fx, px, tx)	No correlation between age and course of illness	Higher plaque counts in the patients with NF; no correlation with the severity of dementia
Terry et al. (1991)	15	?	79 ± 9	p; C	Pl, NF, neurons (fx, px)		AD; weak correlation between Pl or NF and cognitive findings (close correlation between cognition and synapse density)
Wilcock and Esiri (1982)	35	0,8 : 1,2	79	p; C	Pl, NF (fx, px, tx, ox,		Close correlation between the stage of dementia and NF, weak correlation with Pl in neocortex and hippocampus

[a] non-demented patients have been included in the statistical analysis
p = prospective; r = retrospective; C = control group; (AD) differences between patients with AD and the control group: ↑ Pl, ↑ NF, ↓ neurons; fx, px, tx, ox = frontal, parietal, temporal and occipital cortex

A neuropathologist can "diagnose" AD with high probability in the case of severe AD brain lesions in severely demented cases, but he has a smaller chance of "diagnosing" dementia in mildly-to-moderately demented cases than a clinician, who has a greater change of "predicting" AD lesions on the basis of the clinical state of the patient (Crystal et al. 1988). Thus, the diagnostic power of neuropathology in investigating brian atrophy, plaques, and tangles is generally overestimated. Duyckaerts et al. (1990) showed the high variance in the interpretations of neuropathological findings in two controls and two mildly demented cases among 11 European neuropathological laboratories. This unexpected weakness of neuropathological counting procedures can be improved by the measurement of cell loss, cell atrophy, or synaptic breakdown (DeKosky and Scheff 1990; DeKosky et al. 1993; Terry et al. 1991; Weiler et al. 1990).

Correlations between the severity of clinical and neuropathological change

If one believes in a relationship between the mind and the brain, it is not unreasonable to assume that there should be a correlation between the severity of clinical impairment and the severity of neuropathological change. The findings of Gellerstedt (1933), who demonstrated degenerative change in the mediotemporal lobes of non-demented elderly individuals, warned against oversimplifications and discouraged the search for close clinico-pathological correlations in AD. Roth and coworkers have made a great effort to resuscitate this line of research and to demonstrate a statistical correlation between clinical dementia scores and cortical plaque counts (e.g., Blessed et al. 1968). Correlations can also be found between cognitive performance during the last year of life and gross anatomical measurements, e.g. of brain weight or neuron counts (Förstl et al. 1993). Very high correlations have recently been described between cognitive impairment and decreased synaptic density in brain biopsies (DeKosky and Scheff 1990; DeKosky et al. 1993; Terry et al. 1987). It has been suggested that a loss of synapses is a relevant correlate of the clinical deficits in a variety of dementing illnesses, whereas amyloid deposition is a marker of the underlying disorder, AD (Zhan et al. 1993).

A number of clinico-pathological postmortem studies is summarized in Table 4. Either the study design or the clinical, neuropathological, or statistical approaches in some of these investigations were flawed and thus their results or conclusions are difficult to compare. Thirteen of 21 studies listed in Table 4 were prospective and some of them showed significant correlations among clinical findings, mostly between the Blessed scale (Blessed 1968) and histopathology, usually estimates of plaque density. This yield is modest considering the large number of possible comparisons and correlations:

- clinical variables: diagnosis, duration of illness, severity of illness, behavior rating scales, cognitive test scores, etc.,

Table 5 Suggested clinical and neuropathological concepts of Lewy-body disease

Reference	Suggested term	Dementia	Dysphasia, apraxia	Confusional states	Fluctuating course	Halluci-nations	EPMS	Plaques	Neuro-fibrillary tangles
Burkhardt et al. (1988)	DLBD	+				+	(+)	(+)	(+)
Byrne et al. (1989)	DLBD	+	+		+			(+)	(+)
Clark et al. (1986)	LBD	+	(+)	(+)	(+)			(–)	(–)
Crystal et al. (1990)	DLBD	+				+	+	+	+
Dickson et al. (1989)	DLBD	+						+	–
Gibb et al. (1989)	CLBD	+	+					+	+
Hansen et al. (1990)	LBVAD	+	(+)				+	+	+
Heilig et al. (1985)	0	+				(+)	(+)	(–)	–
Perry et al. (1990)	SDLT	+		+	+	+	(+)	++	(–)

LBD = Lewy body disease; DLBD = diffuse Lewy body disease; CLBD = cortical Lewy body disease; LBVAD = Lewy body variant of Alzheimer's disease; SDLT = senile dementia of the Lewy body type; EPMS = extrapyramidal motor symptoms

Table 6 Demographic and clinical features in three clusters of patients with verified Alzheimer's disease

Cluster	High neuron counts	Low hippocampo-parahippocampo-parietal counts	Low coeruleo-frontal counts
n	12	11	14
Age of onset (years)[a]	77 (60–87)	80 (64–88)	72 (58–90)
CAMCOG[a, b]	21 (0–46)	10 (0–57)	7 (0–57)
Depression	4	1	4
Delusion/hallucinations	3/5	1/3	1/1
Grasp reflex	2	3	5

[a] Median (range); [b] maximum 107; worst score 0 (Roth et al., 1986)

- confounding variables: age, gender, education, etc.,
- neuropathological features: plaques/β-A4 deposits, neurofibrillary tangles, neurons, synapses, transmitters, etc.,
- brain areas: and
- staining or counting methods.

Various strategies have been employed to investigate the statistical correlations between quantitative clinical and quantitative neuropathological change. A large number of cases, good reliability of clinical and neuropathological measurements, avoidance of ceiling and floor effects of the test instruments, and use of biopsy tissue instead of autopsy material with long time intervals between clinical testing and postmortem measurement have frequently led to high correlations. Increasing the number of correlations without correcting for repeated tests, using parametric statistics for non-parametric data, and the inclusion of "controls" whose clinical and neuropathological data are necessarily different, are questionable strategies that tend to yield high correlations. The inclusion of a sufficient proportion of severely demented cases – as found in most "biological research samples" but not in epidemiological studies – tends to increase correlations (Fischer et al. 1991). To date, there are no published population-based studies in this field, but a number of such projects are currently under way. As interindividual variations are high, it was not surprising that no significant correlations were found in studies on small case numbers using conservative corrections for multiple comparisons. A recent study did not find increasing plaque and tangle counts from biopsy to autopsy (20 to 48 months later) (Bennett et al. 1993). Early lesions tend to correlate poorly, whereas high correlations can be found for late lesions.

Subtypes of Alzheimer's disease

The clinical and neuropathological heterogeneity of AD has often been explained by the existence of "subtypes" of the disease. Examples of clinical subtypes are senile/presenile, familiar/sporadic, aphasic/non-aphasic, rigid/non-rigid, myoclonic/non-myoclonic, and other forms of AD. Suggested neuropathological subtypes have been charac-

Table 7 Focal brain atrophy with Alzheimer plaques and neurofibrillary tangles

Reference	Patient ♂ : ♀	Age	Early symptoms	Predominant symptoms	N'pathological findings/diagnosis
Berthier et al. (1991)	1♀	48 (onset)	Slowly progressive visual impairment andagraphia	Mild to moderate cognitive impairment	Biopsy: AD (Area 7); "posterior cortical atrophy"
Brun and Gustafson (1991)	0 :4	(69–83)	"Frontal lobe dementia" with early personality change, euphoria, impaired insight, dysphasia, dyspraxia, agnosia and rigidity		AD with frontal accentuation
Crystal et al. (1982)	1♀	57 (onset)	Left-sided astereognosia, hemisensory deficit, choreoathetosis	Decreased short-term memory, mild aphasia	Frontal lobe biopsy: AD
Faden and Townsend (1976)	1♂	72	Visual impairment, blindness myoclonus, confusion, aphasia	Increasing memory impairment, tangles	Cortical plaques and neurofibrillary
Hart and Gordon (1990)	1♂	39	Rigidity, dystonia, choreatic finger movements, grimacing	Dementia	AD (+ Gerstmann-Sträussler-Scheinker-disease?)
Hof et al. (1989)	6 ♂/♀	79 ± 8	Balint' syndrome (optical ataxia, ocular apraxia, simultaneous agnosia)	Diagnosis: AD	AD with increased plaque- and neurofibrillary density in area 17 and area 18 and lower density in the frontal lobes
Jagust et al. (1990)	1♀	74	Left-sided hemiparesis	Dementia	Plaques, neurofibrillary tangles and neuronal loss in the somatosensory cortex right > left
Morris et al. (1984)	1♂	64	Aphasia, right-sided hemiparesis	Mutism, dementia, rigidity	AD with left fronto-temporal atrophy
Pogacar and Williams (1984)	?	?	Aphasia	Dementia	AD, accentuated around the left Sylvian fissure

terized by the presence or absence of tangles, amyloid angiopathy, and other white matter involvement, spongiform changes, Lewy-bodies, severe neuronal loss in the locus coeruleus, and by other features.

Several authors felt that Lewy-bodies in the cortex and brainstem of demented patients represent the hallmark of a distinctive disease or a specific variant of AD. The clinical and neuropathological characteristics associated with this surmised Lewy-body disease vary considerably from study to study and even conflict (Table 5). In the IoP study, patients with AD and cogwheel rigidity had lower neuron counts in the substantia nigra and a higher prevalence of Lewy-bodies in the brainstem and neocortex (Förstl et al. 1992, 1993), but there was no evidence to suggest that this was more than a mere coincidence of AD and Parkinson's disease.

Bondareff and coworkers (Bondareff and Mountjoy 1986; Bondareff et al. 1987; Bondareff et al.1993) found a relationship between neuronal loss in the locus coeruleus and greater severity of illness, whereas Zubenko and Moossy (1988) and Zweig and coworkers (1988) described a more specific association with depression in AD. The latter is in agreement with data from the IoP study. A factor analysis on these data revealed an association between neuron counts in the locus coeruleus and in the mediofrontal lobe (factor I) and another statistical relationship between neuron numbers in the hippocampus (area CA 1), parahippocampal, gyrus, and parietal lobe (area 7). This may be interpreted as evidence for a hippocampal-parahippocampal-parietal pathway and a separate coeruelo-frontal pathway of neurodegeneration. Further evidence for this potential frontal/temporo-parietal dichotomy can be adduced from functional neuroimaging (Haxby et al. 1988; Jobst et al. 1992; Mann et al. 1990). A cluster analysis based on the neuron counts in the frontal lobe (area 32), parietal lobe (area 7), parahippocampal gyrus, hippocampus (CA1), locus coeruleus, dorsal raphe nucleus, and substantia nigra of 37 patients led to three different groups (Table 6). Cognitive performance was best in the group with the highest neuron counts in all brain areas, and four of these 12 patients had depressive disturbances. The group with low hippocampo-parahippocampoparietal counts showed severe cognitive impairment. Depressive features and "frontal lobe signs" were common in the group with low coeruleo-frontal neuron counts. However, such post-hoc analyses tend to yield patient "clusters," whose existence and importance need to be established using independent patient samples. Depression in AD does not usually increase with greater severity of dementia, as would be expected if its cause were purely degenerative, but tends to decrease during the stage of moderate dementia. This may be explained by a decrease of reactive disturbances (Fischer et al. 1990).

Table 7 lists some examples of extraordinary single cases or small series of patients with distinctive clinical features and focal degenerative change in the corresponding neuroanatomical areas. "Slowly progressive aphasia," "frontal lobe degeneration," and several other neuropsychological or psychopathological features have been described in patients who eventually developed Alzheimer plaques or neurofibrillary tangles. This demonstrates that focal brain atrophy is not necessarily associated with

other specific histopathological features, for example Pick bodies or spongiform change (Baldwin and Förstl 1993). These highly selected cases represent extremes that can be expected in a disease or group of diseases as common and heterogeneous as AD.

Conclusions

A clinical diagnosis of AD following strict criteria can be verified by standard neuropathological criteria in a large percentage of cases, and this neuropathological verification remains an important measure of quality control. It should not be forgotten that there is no single, absolutely reliable or qualitative neuropathological marker, no "gold standard." There are, however, conflicting criteria and biased studies on often highly selected patient samples showing impressively high diagnostic accuracy.

The complexity of potential correlations between clinical and quantitative neuropathological findings and the degree of interindividual variance have prohibited truly convincing findings that would have surpassed the expected. Research still has to grapple with great methodological problems on both the clinical and neuropathological sides of such studies. Some of the simpler problems can be characterized as floor or ceiling effects affecting clinical instruments and possibly also as the biological disease process in the late stage of illness. Others have to do with the sheer number of parameters of uncertain pathophysiological significance and with the large interindividual variability.

Clinical and pathological subtypes or "clusters" can be defined easily in any heterogeneous group of diseases. Such attempts may become important, as they may help us to identify patients who will respond favorably to differential treatment strategies. Such efforts are less than convincing, however, if no relevant correlations between clinical and biological features can be shown or if the suggested "subtypes" simply represent extreme variants of a heterogenous disease.

The neuropathological examination of the brain will lose none of its importance in dementia research if it adopts new molecular biological techniques. Comparison with advanced neuroimaging methods will permit new insights into the natural course of neurodegeneration. Some of the most puzzling problems can only be solved if clinicians and neuropathologists increase their awareness of methodological limitations. A number of clinicopathological correlations found were fairly predictable on the basis of the case definitions employed. One of the most demanding strategies to overcome of the most disturbing artifacts is the study of epidemiologically representative samples from an aging population. It would not be surprising if some of the seemingly clear-cut margins between cases and controls became blurred in such studies and if the particularly interesting and outstanding cases were clearly visible as the tips of icebergs.

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