Th ere was a time (up to the 1960s and 1970s) when few would have questioned that a neuropathological exami-
nation of the brain at autopsy was needed to make a
diagnosis of Alzheimer’s disease (AD). Th is was at a time
when clinical diagnostic instruments and neuroimaging
were in their infancy. It was also a time when dementia
was clinically divided into pre-senile and senile forms
and the AD pathological label was applied most confi-
dently in pre-senile cases. Much has changed since then,
and it is appropriate to ask whether neuropathology is
still the gold standard by which to reach such a diagnosis.

Many cases of clinical AD are correctly diagnosed in life
if the person concerned is seen by a specialist with much
experience of the condition. Th e proportion of cases
correctly diagnosed will continue to climb if specialists
have access to advancing imaging and other diagnostic
procedures. Th e situation is different, however, if the diag-
nosis is made by someone without specialised knowledge
or without access to state-of-the-art investigations.

Even among cases seen by specialists there will be a few
that defy a correct diagnosis either because they present
atypically or because a rare disease is masquerading as
clinical AD. I have seen both. Frontotemporal dementia
and AD can sometimes be indistinguishable until micro-
scopic sections have been examined. Th ese cases cannot
be correctly diagnosed without recourse to the micro-
scope, and even then may fail to fit criteria for a
diagnostic label. Only through the careful pathological
assessment of such cases, however, often assisted by new
pathological techniques (for example, new antibodies,
genetic probes), will progress in delineating new or newly
recognised diseases evolve.

Although it may at present only be in the minority of
cases that neuropathology is required to attach the
correct diagnosis to a case of dementia, it can be diffi  cult
to predict in life which cases will fall into this category.
Furthermore, diseases change and evolve over time. One
hundred years ago it was possible to clinically confuse
AD with tertiary syphilis but pathology provided a ready
distinction. Now it is more likely that confusion might
arise with respect to AD and AIDS-related dementia.
Where will the confusion come from in the future? We
need to remain watchful for novel forms of disease
arising, and we need look no further than new variant
Creutzfeldt–Jakob disease to be reminded of this.

Affixing a single, specific diagnostic label, whether at
the clinical or pathological level, is generally more easily
achieved in young patients in whom the brain succumbs
to a single pathological process. Th e difficulty with AD is
that it is a condition whose incidence rises exponentially
with age [1] when multiple factors may contribute to
cognitive decline. Th ese are likely to be different in
different individuals and not all of them can yet be
apportioned their real share of blame. Hence, unitary
diagnoses are much less likely to apply. It was through
pathological studies that we were made aware of how
much cerebrovascular disease, particularly small vessel

**Abstract**

Recent advances in the clinical diagnostic instruments
for diagnosing Alzheimer’s disease (AD) and in
neuroimaging may cast doubt in the minds of
some practitioners about the continued need for
neuropathology to provide the ultimate diagnosis.
Certainly the majority of cases of AD can be clinically
correctly diagnosed by experienced clinicians but
many cases are given this label by less experienced
practitioners. Even after the most thorough work-up,
a few cases of confidently diagnosed AD turn out to
be something else when microscopy of the brain is
undertaken. Even for neuropathologists, however, it
can be difficult to correctly assign cognitive decline
to the various pathological processes that can be
found together in an older brain. We need further
clinicopathological study to enlighten us about, for
example, the contribution of commonly found
cerebrovascular disease to dementia. Human studies
are also needed to explore the changes in pathology
that new treatments for AD may produce.
subcortical disease, and AD pathology co-exist [2]. True, vascular disease can now be assessed quite well with neuroimaging, but we still lack thorough understanding of exactly what contribution cerebrovascular disease makes to cognitive impairment [3].

We still need well-designed clinicopathological studies to acquire a much better understanding of the complexities of the pathological basis of cognitive decline in the older person and the many factors that feed into the clinical expression of pathological disease. Pathological examination of the brain provides a much more secure foundation on which to base understanding of the cellular and molecular changes that contribute to dementia, including AD, than do clinical and imaging data. Community-based studies have shown us how misleading can be the impression of rather stereotyped disease that is gained from case-control cohorts. Unbiased (blind to cognitive function) pathological assessment of brains from a random community sample of older subjects – such as is provided in the UK by the Medical Research Council Cognitive Function and Ageing Study (www.cfas.ac.uk) – enable us to appreciate how variable is clinical expression of AD pathology [4-6]. Such studies indicate the need to uncover the factors that enable someone with well-developed pathological features of AD to perform perfectly well in activities of daily life. Such knowledge will be essential given the massive rise in the world’s older population.

Until we have reliable biomarkers that enable a confident diagnosis of AD to be made in life, which reflects the pathological basis of this disease, an autopsy examination of the brain remains an essential tool. With all due respect I would venture to say that we delude ourselves if we think we can reach a molecular understanding of this still enigmatic disease without an opportunity to explore cellular and molecular changes in affected human brains. Furthermore, it is essential to study at autopsy the brains of people who have participated in clinical trials, since this is the way to gain clarity over whether the treatment manages to abolish the pathology. Examination of a meagre eight cases treated with the initial anti-β-amyloid manages to abolish the pathology. Examination of a fraction of people who have participated in clinical trials, since neuropathology no longer has a part to play in helping to diagnose and understand AD, but that time has not yet come and, in my opinion, is likely to be a good way off. Autopsy examination of well-studied cases of AD and other dementias still has a critical role to play.

Abbreviations

AD, Alzheimer’s disease.

Competing interests

The author declares that she has no competing interests.

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