

## Editorial

**Longitudinal Epidemiologic Clinical-Pathologic Studies of Aging and Alzheimer's Disease**David A. Bennett<sup>1,2</sup> and Lenore J. Launer<sup>3</sup>

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Clinical-pathologic studies have had an enormous impact on our understanding of aging and the conditions that lead to loss of cognitive and motor function in advanced age. In the mid to late 19<sup>th</sup> century, clinical-pathologic studies of persons with dementia demonstrated atrophy and a reduction of brain weight, which were thought to result from 'hardening of the arteries' [1]. Senile plaques were first identified by Blocq and Marinesco in 1892 but these investigators did not make the link to dementia [2]. However, in separate papers in 1906, Alzheimer and Fischer each reported that senile plaques and neurofibrillary tangles were associated with dementia [3, 4]. In 1910, Kraepelin introduced the term Alzheimer's disease (AD) in his textbook of psychiatry referring to a relatively rare cause of pre-senile dementia that was thought to be something quite distinct from senile dementia which resulted from hardening of the arteries [5]. The distinction between pre-senile and senile dementia lasted six decades until an elegant series of papers by Tomlinson, Blessed and Roth demonstrated that senile plaques and neurofibrillary tangles were also a major cause of senile dementia [6-9]. Clinical and pathologic criteria for AD introduced in the mid 1980s set up a clinical-pathologic dichotomy in which the clinical diagnosis of AD required no evidence of known factors (including cerebrovascular disease) that may lead to dementia (i.e., a diagnosis of exclusion), and the pathologic diagnosis which required a moderate number of neocortical neuritic plaques [10,11]. Almost immediately, two studies published in 1988 challenged this dichotomy by identifying people without dementia during life who had significant AD pathology at autopsy [12, 13]. Thus, it became clear that a complete picture of AD would require the clinical study of people with a wide range of cognitive functioning, especially persons without dementia, who subsequently come to autopsy. Early efforts to assemble such a sample met with limited success. For example, between 1987 and 1995, the Consortium to Establish a Registry for AD (CERAD) which included 24 federally funded AD centers from across the United States conducted only 8 autopsies out of 25 deaths among those recruited without dementia [14]. It was clear that federally funded AD centers established at tertiary care medical centers had much expertise to contribute to the study of aging and AD, but their capacity to secure large numbers of autopsies from persons without dementia was limited. The need for such data led to the realization that community-based autopsy series could play a critical role in understanding AD, and more broadly, dementia-causing pathology, in addition to other age-related conditions associated with morbidity and mortality including parkinsonism and loss of motor function.

The careful study of clinical patients that came to autopsy has led to many important advances for clinical-pathologic research, including the development of immunostains for neurodegenerative markers including amyloid- $\beta$  and paired helical filament tau for AD pathology, ubiquitin and subsequently  $\alpha$ -synuclein for the identification of Lewy body pathology, and more recently TAR DNA-binding protein 43 (TDP-43) [15-19]. However, over time the importance of cerebrovascular disease, especially microvascular disease became clear – but because many studies of carefully selected patients excluded people with evidence of vascular disease, these lesions could not be well studied in most existing autopsy samples. Further, as some of these lesions cannot be quantified by neuroimaging [20, 21], or examined in association to ante-mortem cognitive change or adverse health outcomes, the study of neuropathology needed to be broadened to include community-based samples. Also, with the increasing realization about the heterogeneity of pathology in the brain, there was a move toward quantifying the load of different types of lesions and using quantitative analytic epidemiologic approaches (e.g., multi-variable analyses) to understand how these lesions were related to dementia, with less emphasis on providing categorical diagnostic information. Thus, autopsies from community based samples have provided novel and critical insights into the pathology of the aging brain. Thus, the large numbers of autopsy samples brought epidemiologic principles to the characterization of the brain including highly standardized recruitment of subjects, archiving and evaluation of the tissue samples, and rich ante-mortem phenotype data that can be examined in association with quantitative measures of neuropathologic lesions.

This special issue of *Current Alzheimer's Research* highlights findings from several longitudinal epidemiologic clinical-pathologic studies of aging and AD. Two studies are noteworthy for having introduced this methodological approach. The first is the Nun Study, led by Snowdon and colleagues, which was the first community-based prospective cohort study of aging and dementia that required organ donation [22]. The second is the Honolulu Asia Aging Study (HASS), led by White and colleagues, which was the first population-based prospective study of aging and dementia that had a fully standardized autopsy component leveraged onto the cohort [23]. These two studies initiated in the early 1990s inspired several others, many of which are brought together in this special issue. The studies have three things in common. First, they are all community- or population-based, meaning they do not recruit participants based on contact

with the health system for cognitive complaints or carefully screen potential participants based on pre-determined clinical criteria, as is the typical recruitment strategy from tertiary care medical centers. Population-based refers to a geographically defined population whereas community-based refers to other cohorts of convenience. Second, they are all fundamentally epidemiologic cohort studies. Third, the investigators have all incorporated standardized neuropathologic measures evaluated quantitatively and blinded to clinical diagnosis into the fabric of their epidemiologic approach. Together, these characteristics allow the results from community-based clinical-pathologic studies to challenge conventional dogmas leading to novel insights into the causes of aging phenotypes. This special supplement is not an exhaustive compilation of such studies but should be considered representative of the genre [24-30].

The special issue leads with three articles that focus on community-based cohort studies that require agreement for organ donation as a condition of entry. The first is an article by Mortimer which reviews the history of the Nun Study and highlights several of its key findings [31]. This is followed by two articles by Dr. David Bennett and colleagues which provide a comprehensive review of findings from the only other two cohort studies that require organ donation: the Religious Orders Study and the Rush Memory and Aging Project [32,33]. The three studies differ in their strengths and weaknesses. Two notable features of the Nun Study are the fact that they represent a single Catholic order of women over age 75, and that they were recruited as a birth cohort, i.e., all sisters born between specific years at the initiation of the study. The Religious Orders Study was intended to complement the Nun Study by enrolling men in addition to women, racial and ethnic minorities, a younger age from multiple orders, without known dementia at baseline. However, the study was still restricted to Catholic nuns, priests, and monks. The Rush Memory and Aging Project was intended to complement the prior two studies by enrolling lay persons and enriching the numbers of participants with 12 or fewer years of education to evaluate a broader segment of the population. Further, the Rush Memory and Aging Project also required agreement for donation of the entire spinal cord, and selected muscles and nerves to serve as a source of clinical data and biospecimens to support studies of central and peripheral motor and sensory systems. All three are studies of a convenience sample whose strengths come from the internal validity achievable through high follow-up and autopsy rates. This is important as persons who drop out or refuse organ donation differ from those who agree. However, these are not population-based and other studies are needed to support the generalizability of findings from these cohorts. Further, as individual population-based studies are representative of a particular community, multiple population-based studies are also needed to support generalizability.

The next section summarizes findings from five population-based cohort studies with autopsy, three from the United States and two from the United Kingdom. These cohorts represent persons recruited from geographically defined populations. The first article in this section is by Gelber and colleagues providing the background and selected findings from the Honolulu Asia Aging Study [34]. A unique feature of the study is that it added a dementia component and au-

topsies in 1991 to the Honolulu Heart Program which began in 1965. Thus, unlike the three cohort studies described above, the study can relate risk factors directly measured in mid-life to brain pathology. Further, the study has accumulated several hundred brains, more than any other population-based study with autopsies. However, the study only includes Japanese American men. The next article, by Au and colleagues, provides findings from the Framingham Heart Study [35]. The Framingham Heart Study is even older than the original Honolulu Heart Program cohort of the HAAS, having started in 1948 with the dementia component starting in 1976. Multiple generations men and women now participate. However, the autopsy component is relatively recent with about 100 autopsies. Next are articles about two studies by Richardson and colleagues. The first article shares data from the Medical Research Council Cognitive Function and Ageing Study, a six-centre longitudinal population-based study of people over age 65 years in England and Wales which started in the late 1980s [36]. The autopsy study was added in the early 1990s. The investigators have managed to accrue well over 400 autopsies. The next article paper gives results from the Cambridge City over-75s Cohort [37]. It began in the mid 1980s and now has more than 200 autopsies. This article is more focused on an important public health question and highlights the contribution of microvascular pathology to falls. Falls along with the broader problem of gait and motor dysfunction in the elderly has been markedly understudied from the vantage of clinical-pathologic relationships. The final article in this group by Corrada and colleagues highlights findings from the 90+ Study which began in 2003. This study draws on the survivors of the Leisure World Cohort Study, started in the 1980s and located in a retirement community in Orange County, CA [38]. Similar to some other studies, it has the ability to link mid-life risk factors to brain autopsy findings. Importantly, it is a large study with autopsies acquired on the oldest old. These five studies are all leveraged onto a defined population base. Any bias that may arise in the recruitment of subjects into the autopsy study can be studied within the parent cohort, which is much more representative of the community.

The next article, by Montine and colleagues, summarizes key findings from the Adult Changes in Thought Study, which is an example of leveraging an autopsy sample onto a large Health Maintenance Organization, Group Health Cooperative, which serves the Seattle Washington area [39]. The advantage of this approach is the availability of extensive medical records and a pharmacy database that dates back for many years allowing unique linkages to autopsy findings. The following article is by Schmitt and colleagues on the Biologically Resilient Adults in Neurological Studies [40]. This study represents a more traditional approach for recruitment of volunteers that has been taken by one of the federally funded Alzheimer's Disease Research Centers.

The final article in the special issue by Barnes and colleagues highlights efforts in the African American community, which bring together participants from the Minority Aging Research Study in addition to African Americans participating in the Religious Orders Study and the Rush Memory and Aging Project [41]. Unlike the other papers which highlight findings from analyses of clinical-pathologic data, this paper highlights the challenges of obtaining autopsies in

the African American community and the approach taken by one group of investigators. Such efforts are needed as increasing evidence raises the possibility that clinical-pathologic relationships may differ among African Americans and whites. Similar efforts are also needed in the Hispanic community along with other racial and ethnic minorities. Such efforts should start soon, as successful efforts in these communities are likely to require extensive and persistent interactions between study personnel and the community to build trust and understanding. For example, both the Religious Orders Study and Rush Memory and Aging Project have recruited African Americans and Hispanics and tested in Spanish when required for many years. However, the numbers of participants and autopsies from Hispanics remain far too few for meaningful clinical-pathologic comparisons.

Together, despite the differences in methods, cohorts, and approaches, the studies report a number of relatively consistent findings that have markedly advanced the field of age-related cognitive and motor function. First, among older persons who represent the vast majority of people with dementia in the United States, United Kingdom, and other developed countries, multiple conditions contributing to dementia is the norm. Thus, strategies to prevent dementia, the most logical response to a public health problem of this magnitude, will require interventions targeting a range of pathologies, in addition to amyloid deposition and tangle formation. Second, the implication of mixed pathologies is that some risk factors for clinical AD will be risk factors for co-morbid conditions rather than risk factors for amyloid deposition and tangle formation. The ability to link risk factors to incident clinical disease and post-mortem neuropathologic indices is a powerful approach to decoding biologic pathways linking risk factors to disease. Understanding such pathways is essential for the rational development of interventions. Third, among the oldest old, those over the age of 85, and the group that is growing most rapidly in the United States and other developed nations, AD pathologic changes remain important, but other pathologies become relatively more important suggesting that a much better understanding of the causes of dementia in the oldest old are needed. Fourth, the findings demonstrate that it is hard to get old and escape the accumulation of common pathologies of aging. However, one can get old without development overt dementia, despite the accumulation of pathology. This should not be interpreted as the pathologies being measured are less important than first thought. Rather, there are protective factors related to reserve and resilience. They allow people to get old, accumulate pathology, but not develop dementia. These protective factors need to be much better understood as they are potential therapeutic targets. Fifth, the pathologies that lead to cognitive decline and dementia are also leading to dysfunction in motor and sensory systems and these can occur prior to the onset of dementia or mild cognitive impairment. Therefore, it is limiting to define AD solely by its effect on cognition. Like other pathologies which affect cognition, motor function, and behavior (e.g., cerebrovascular disease, Lewy body pathology) the manifestations of AD likely depend on the anatomic location in addition to the severity of pathology. Sixth, AD is developing in a brain that has a life history and other brain pathologies; the brain is accumulating pathology in a body that is experienc-

ing dysfunction in many other physiologic systems (e.g., cardiopulmonary, renal). The ability to address these myriad factors which may include recursive processes in the same individuals offers opportunities to greatly improve our understanding of age related decline in cognition and other systems. Seventh, the cohorts allow the use a systems biology approach to link next generation “omics” data such as epigenomics and RNA sequencing on brain tissue to risk factors, and repeated measures of quantitative phenotypes. This is a powerful means to identify truly novel therapeutic targets in a hypothesis free manner using the tissue that is most relevant to the cognitive aging process. Lastly, the incorporation of brain pathology into epidemiologic studies is a major advance in the use of clinical-pathologic studies, which have made and will continue to make important contributions to our understanding of AD and other age-related neurologic diseases. These studies have all been largely supported by public funding agencies in the United States and Europe. As is evident from this collection of papers, these resources are extremely valuable and should be maintained and remain accessible to future scientists.

## CONFLICT OF INTEREST

None declared.

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