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GUEST EDITORIAL

What should we do if we were wrong and Alzheimer was right?

For more than 2,000 years cognitive decline and dementia were considered a part of aging, like graying of hair, wrinkling of skin, or (more recently) reduction of pulmonary capacity or glomerular filtration rate. Thus, our recent predecessors considered "senile dementia" a normal consequence of the aging process. Their confidence increased after Martin Roth and colleagues added specificity to the concept by differentiating it within the broader category of "senile psychosis" (which, consequently, became obsolete). A diagnosis of "Alzheimer's pre-senile dementia," by contrast, was reserved for people with earlier onset of dementia.

This distinction between pre-senile dementia (a disease) and senile dementia (a feature of aging) was gradually abandoned following observations, again by Roth with Tomlinson and colleagues (Blessed *et al.*, 1968) and championed by Katzman (1976) and Terry (1978). These men saw what others had noted earlier (Alzheimer, 1911; Newton, 1948; Lauter and Mayer, 1968) that the brains of patients with the two disorders appeared strikingly similar. Thus, the 1970s and 80s saw a true paradigm shift as "senile dementia of the Alzheimer type" was recognized as every bit as much a disease as the rarer pre-senile forms. Skeptics were won over by compelling demonstrations of nonagenarians and centenarians who may have been "senile" in other ways, but certainly did not have dementia. "Alzheimer's disease" (AD), as the condition came to be known generically, could provoke dementia at almost any age, but it was not a part of normal aging. The final victory for the new paradigm came a decade later with triumphs of molecular biology. The gene for the amyloid precursor protein was cloned and sequenced; various Aβ and other cleavage products (and their aggregates) were identified; and several splice and phosphorylation variants were discovered for the microtubule associated protein *tau*, the precursor of neurofibrillary tangles. All of these were characteristic of "Alzheimer's disease," no matter how young or old the patient.

Over the last 30 years, this new disease paradigm brought strong efforts to investigate the causes of all types of age-related dementia. It is difficult to overstate the value of the resulting research, most of which probably would not have occurred in an environment that regarded AD as nothing more than a phenomenon of aging. And there has indeed been some progress. However, in clinical terms at least, this progress has been painfully slow. Now may be a time, therefore, to re-examine our assumptions and shared perspectives in light of important (but sometimes overlooked) epidemiological data and their implications.

Know your enemy: what is the cumulative incidence of AD dementia by age?

Surprisingly, the literature offers little information on this topic. Several articles have attempted to estimate populations' lifetime probability of dementia onset *before death* (e.g. Seshadri *et al.*, 1997; Ott *et al.*, 1998; Yu *et al.*, 2010). In each of these papers, the cumulative risk of disease is conditioned on staying alive. That is a topic of some interest, as it asks the question, "if I am a man (or woman) currently at age x, what are the chances that I will succumb to dementia before I die?" The answer obviously depends in part on one's estimate of conditional life expectancy at age x. The latter can vary widely based on factors unrelated to a person's tendency otherwise toward dementia.

By contrast, some years ago my colleagues and I approached the cumulative incidence question a bit differently. We wanted to explore the influence of *APOE* genotype on AD risk in a large population (Khachaturian *et al.*, 2004). We sought particularly to know whether the risky ε4 allele increased the proportion of the population susceptible to AD dementia, or whether it simply accelerated events that would otherwise occur later. Thus, we needed an estimate of cumulative incidence in the population *overall* as well as an understanding of whether this estimate differed by genotype.

In the unusually long-lived Cache County population, we obtained data on AD incidence across a broad range of ages. We began by asking what proportion of the population would develop AD dementia by age 100 years, *assuming that they survived other, competing risks to this age* (i.e. ignoring mortality and competing risks). We next explored the influence of *APOE* genotype on this proportion. Findings on the first question are reproduced

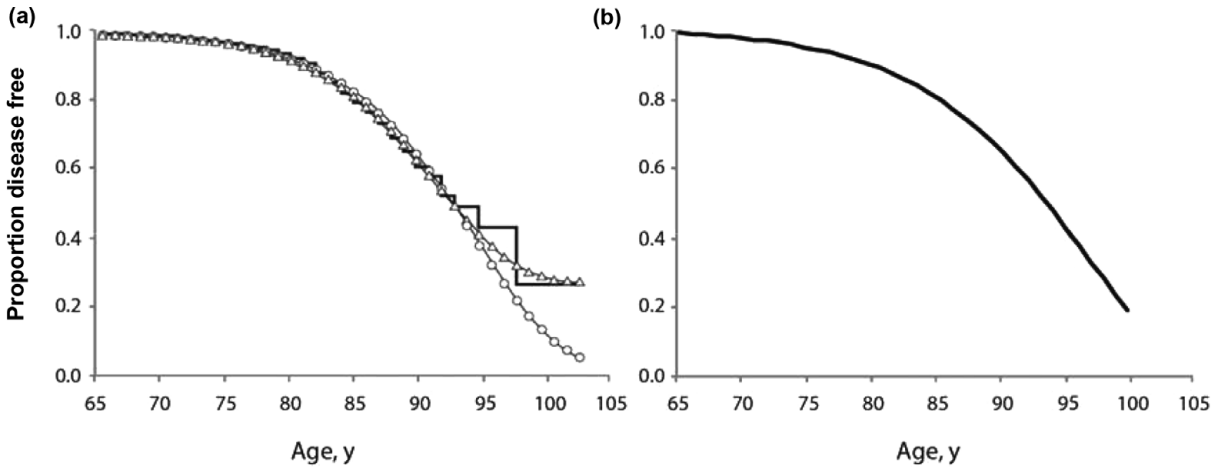

Figure 1. (a) Estimates of disease-free survival in the Cache County population. The figure shows Kaplan-Meier empirical survival estimates (sawtooth lines) and two Weibull models (smooth lines) fitted to the data. One Weibull model, with open circles, assumes that age-specific risk of AD onset is homogeneous, i.e. that there are no subgroups with substantially different characteristic risks-by-age. The other model, shown with open triangles, incorporates a parameter corresponding to a proportion of the population that will not develop dementia at any reasonable age. This second model gives a vastly improved fit to the data (Khachaturian *et al.*, 2004). As a result of the admixture of ostensibly invulnerable individuals (in reality, they may only have a much later onset characteristic), the latter curve approaches an asymptotic value at the proportion of those estimated in the model as being not at risk (approximately 25%). For several reasons cited in the text, that estimate is likely to be substantially inflated. (b) The figure shows the disease-free survival (1 – cumulative incidence), as estimated from the exponential equation fitted by Brookmeyer *et al.* (2007) to data from several well-regarded cohort studies of AD incidence. This curve appears quite similar to the Weibull models in Figure 1(a), although it makes no attempt to discern heterogeneity. Both Figures 1(a) and (b) suggest that the large majority of individuals may be expected to develop AD dementia if they survive to age 100 years. Note: Figure 1(a) reprinted with permission.

in Figure 1(a). Apparently, only 28% of persons would remain disease-free at age 100 years. This is equivalent to saying that 72% *of persons would develop AD dementia by this age*. *APOE* genotype did indeed modify the age-specific risk of AD dementia, but its effect was on the *timing* of dementia onset and not on the surprisingly high estimate of lifetime risk *per se*.

As noted above, verification of our cumulative incidence findings in other published material was difficult. We therefore turned to a well-known synthesis by Brookmeyer *et al.* (2007) of data from several high-quality population studies of AD *incidence*. As part of their work, these authors published an exponential equation that provided a best-fit model for the annual incidence of AD as a function of age. The latest iteration of this equation is as follows:

$$Incidence\,(\%\,per\,yr) = 0.117e^{0.127(x-60)}$$

where x is year of age after 60. Using this equation, one can also estimate *cumulative incidence* by calculating the proportion surviving after each year (starting with 100% at age 60), estimating and subtracting the incidence percentage for the ensuing year, and thus arriving at the proportion surviving at the end of that year. Cumulative incidence at age x can then be calculated by repeating this process iteratively up to the year x. This procedure gives results shown in Figure 1(b). Although the latter figure does not include allowance for a stratum of the population not vulnerable to AD dementia (as in Figure 1(a)), both Figures 1(a) and (b) suggest that the cumulative incidence of AD by age 100 years will be around 75%.

The size of this percentage gives me pause. For starters, it is almost certainly an underestimate for several reasons. Survey research on dementia nearly always suffers from: (1) differential response rates with under-representation of persons with dementia (Norton *et al.*, 1994); and (2) differential occurrence of dementia among those who die in the intervals between periodic assessments (Launer and Brock, 2004). Another source of underestimation stems from the substantial numbers of persons (especially in older strata) who have neuropathological "Alzheimer's disease" without cognitive impairment (Bennett *et al.*, 2012). Finally, it is clear that the brains of those with clinical diagnoses of mixed or other dementias frequently include AD pathology.

I therefore suggest that, whatever their true proportion, persons who would reach 100 years without succumbing to AD dementia are a small minority. Alternately stated, *development of dementia in late old age appears to be the norm, and not the exception.*

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Then, is "Alzheimer's disease" really a disease?

The Oxford English Dictionary describes "disease" as a condition in which the body or some of its component parts are functionally deranged or disturbed. Usually, the implication is that the functional disturbance results from an abnormality or process that is not ordinarily expected, i.e. that it is not a change that is ubiquitous for the species. Contrariwise, if the change *does* become ubiquitous with the passage of time, then (by common consensus) it is often considered a part of aging. Importantly, the time-dependent process of change need not proceed at the same rate in all individuals. But it must do so in measurable fashion.

AD and many other late-life diseases challenge this distinction. These illnesses share a characteristic that they evolve over a long period of biological change while remaining largely asymptomatic. Symptoms appear only when the change reaches a certain threshold of accumulated damage. Many years ago, for example, my colleagues and I showed that the probability of AD onset was approximated (in what was certainly an oversimplified model) by an Erlangian or "multiple-hit" distribution (Breitner *et al.*, 1986), such that symptoms became evident only after accumulation of a specified number of "hits." One might then consider whether the chronic accumulation of "hits" (Alzheimerization) is a manifestation of aging, whereas the emergence of symptoms conforms to the notion of disease.

Along with Peter Whitehouse (Whitehouse and George, 2008) and others, I suggest therefore that – for AD at least – the distinction between aging and disease is far from clear. I hasten to add that there can be no doubting the heavy disabilities wrought by AD dementia and the burden it places on families and, ultimately, on society. But, in terms of its origins, my "bottom line" is that, *over a full human lifespan, the development of AD dementia is more the norm than an exception.* The implications of this statement appear to be profound. For those like me with a primary interest in dementia prevention, if development of AD dementia is the norm rather than the exception, then *probably we should not be asking why some people get AD dementia, but instead how or why some few can live a full life and escape it.* Is it possible that these "escapees" manage to avoid dementia onset only by postponing it beyond human life expectancy? We will be able to test this latter idea once we have reliable indicators for the evolving "pre-symptomatic AD" process. Until then it matters not whether, without intervention, most everyone would succumb to AD dementia at some (perhaps very late) age; the objective should be to postpone it. In this way, we may co-opt a favorite expression of the lawyers (about availability of legal remedy). "AD dementia" may be inevitable for most of us, but at some point, with successful interventions, *dementia delayed* may become *dementia denied*.

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