NAXION
thinking

Alzheimer's Disease
Untangling the Paradoxes and the Ironies



By Susan Schwartz McDonald, Ph.D.

Slow Progress, Galloping Prevalence

In 1983, when then President Ronald Reagan designated the month of November as National Alzheimer's Awareness Month, there were roughly two million Americans diagnosed with the disease and no drugs at all approved for treatment. Today, depending on how you count (because the epidemiology remains fuzzy), roughly seven and a half million Americans over 65 are estimated to be living with dementia of the Alzheimer's type, and millions more have mild cognitive impairment (MCI) due to the disease. Also depending on how you count, there are now eight discrete drugs but the only two that qualify as *disease-modifying* – Leqembi (lecanemab) and Kisunla (donanemab) – are not readily accessible or even terribly effective for most patients. The AD crisis is rapidly accelerating, and we are, meanwhile, struggling to make up for lost time with our methods of treatment.

We seem to have done a much better job in identifying new mechanisms and drugs to treat cancer, despite its challenging biologic diversity and complexity—or perhaps *because* of that diversity—and the fact that it was more fully appreciated at an earlier point in the war on cancer. AD took a longer time to capture our full cultural attention and investigational resources, and ironically, when it did, a fixation on beta amyloid discouraged us from giving full consideration to other proteins. We're still dealing with the fallout from politicized protein camps that obstructed progress against the disease. In keeping with how mysterious we still find the brain – our "last-frontier" organ – Alzheimer's (along with other forms of dementia) has proven disappointingly intractable. (See the recent NYTimes article "Will We Ever

Understand Dementia?" for a useful summary of the paradoxical way greater attention to AD also desensitized us to disease nuance and potentially set us back.)

Sorting Through Contradictions

The paradox that people most often point to when talking about AD, officially dubbed "the Alzheimer's Paradox," is used by the popular press to reference the fact that the incidence of dementia appears to be declining even while its prevalence continues to increase. There's some rhetorical flair to that term, but a statistician would challenge the use of the word *paradox* to describe this pattern, whose underlying drivers are moving in different directions but, for reasons easily explained, are not in fundamental contradiction. The increased prevalence of dementia reflects the aging of the population. When the incidence of all-cause dementia is age-adjusted, the reduction reflects a decline in *vascular cognitive impairment* (VCI), which frequently co-occurs with dementia of the Alzheimer's type in a mixed presentation.

The hopeful statistic concerning VCI seems to be the result of improved management of cardiovascular risk factors. There is, however, no persuasive evidence to suggest declining incidence of the pathological process we call dementia of the Alzheimer's type, although the possibility that such evidence will ultimately emerge cannot be ruled out. (Presumably, higher education confers benefits in the form of cognitive reserve that could reduce the incidence of *both* conditions, possibly even other dementias.) For the moment, though, we are looking at two different independent trend lines tangled together at a moment of demographic inflection. The word "paradox" pretends that there is more mystery to this than there is. The real mystery is: what do we do about AD?

Broadly speaking, dementia is an age-related diagnosis and since life expectancy isn't likely to decline in the long term, the proportion of people over 65 will almost certainly remain high, even after the Baby Boomers have made their demographic exit. Given the psycho-social and financial burden of AD, the situation we face is truly catastrophic. A mordantly ironic view of things would suggest that some of the time freed up from many kinds of "work" by AI will ultimately be diverted to the care of family members with AD. If we don't figure this out, we are doomed to be a society of caregivers.

The Struggle to Find Our Bearings on the Road to New Drugs

There is also the demoralizing paradox that removing amyloid plaque seems to have modest *clinical* benefit, even if p-values on primary clinical endpoints suggest *statistical* improvement. That suggests we are chasing after the wrong thing – the thing we can measure and target – or at least that we are doing little more than cleaning up debris after a damaging mess has been

made because we don't yet fully understand the pathology of the disease and we are hard-pressed to reach and arrest the wrecking process actually causing the symptoms.

Then there is the irony that excluding patients with mixed dementia from the trials leaves us with a much smaller population of eligible patients whose narrow diagnosis makes it easier to see results that justify approval, whether or not those results are truly worth the cost and risk incurred. Anyone in this business must appreciate the pressures to chart a straighter line to regulatory approval – and there can be no doubt that the exclusion criteria made these drugs safer as well as easier to assess – but we are left with the unfortunate reality that the drugs developed at great expense and in a spirit of great hope provide modest clinical benefit for an even narrower group of patients who may be too far advanced to benefit. And while our fierce "war on cancer" has benefited from the discovery and pursuit of many mechanisms that can be exploited to thwart tumor growth, we are still looking at limited avenues for drug discovery in AD (e.g., anti-amyloid antibodies and various approaches to arresting tau, including vaccines). When we consider the challenges facing tau strategies, it seems that more immediate additions to the armamentarium are likely to feature convenience and safety more than improved efficacy.

These frustrations come with the AD territory—a daunting terrain that can feel at times like another biological planet. There are the challenges we face in addressing a disease whose biology is not well-understood situated in an organ not easily or safely reached by drugs. And there are the difficulties of diagnosing, staging, and treating a condition whose symptoms are much slower to appear than the physiological disease process underneath and whose sheer breadth and variety confound reliable, sensitive measurement of improvement. Only now, with biomarkers, do we see the prospect of potentially uncovering evidence of the disease process at a stage years before clinical symptoms appear and using more personalized strategies to arrest it. But for investigation of prevention or delayed onset, we are currently too dependent on the slow or unpredictable march of serendipity in the form of observational studies—for instance, the prospect that when looked at in different populations, GLP-1s might yet confer prevention benefits not observed in the recent EVOKE trials. There may be other drugs we can repurpose in hopes of arresting AD in early stages, but it will take time for large-scale natural experiments to run their epidemiological course.

Better Understanding the Stages of the Patient Journey

Meanwhile, there is yet another related challenge that stands in the way of timely therapy. Disease-modifying monoclonals are indicated only for patients considered "mild," which, for the record, includes patients who can perform ADLs but can be so significantly impaired that they have forfeited car keys and lost the ability to follow a narrative plot—in other words, patients who may already be past the point at which they can meaningfully profit from the sort

of amyloid cleanup these drugs are meant to accomplish. *We're still heavily reliant on clinical measurement tests that are sometimes insensitive to actual performance deficits in the world outside the examination room*. There are surely opportunities for improvement in our testing if we want to ensure not only that we understand where patients are earlier in the disease process but also that the therapies of the future target endpoints that matter for patients and their families at each stage.[1] The catch, of course, is that until we are successfully enlisting a broader set of protein strategies, moon shots at many of those clinical endpoints may remain beyond reach. That's not paradoxical, that's fully predictable.

Providing *Timely* Access to Whatever Drugs We Have

And here's more irony. Many private insurers deem the monoclonals "experimental" in light of their modest benefits, and on that basis, opt not to cover non-invasive baseline PET scans needed to qualify for the monoclonals, or to cover the drugs themselves, without great acts of pre-authorization heroism. Practically speaking, therefore, in many parts of the country only Medicare-eligible patients will qualify. The invisible world of pre-clinical disease remains shrouded from view and even very early AD often goes unrecognized or acknowledged, limiting our sightline in this population and our full appreciation of its size. But we can reasonably speculate that, based on very patchy coverage nationwide, many patients younger than 65 and potentially still in the workforce are deprived of access to those therapies at a moment when benefits could be greater. That group may also include early-onset patients likelier to progress more quickly, putting them in more urgent need of early disease-modifying therapy. Either way, these are patients who should not find the door to advanced therapy effectively barred based on insurance alone. Among the many perverse and disheartening ironies or "paradoxes" surrounding AD, this one is clearly contrived by the insurance industry in a spirit of self-interest. It's time payers were taken to task by medical thought leadership and healthcare policymakers.

The enormity of our brain reserves and the extraordinarily adept compensatory mechanisms of the brain make truly early diagnosis difficult – especially when the lack of effective therapy, the gravity of the diagnosis, and the success of compensatory or denial mechanisms deter it. That is the ultimate paradox we need to tackle. The thrust behind biomarker identification needs to be paired with a press for more sensitive clinical measurement, so that we can track early progression from all angles in the service of more effective drug development and can discover therapies that treat the disease as it routinely presents itself, with and without ischemic dementia.

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[1] Carla (DeMuro) Romano et al., "Priorities of People Living with Alzheimer's and Care Partners: What Matters Most?," *Alzheimer's & Dementia* 22 (2026): e71554, https://doi.org/10.1002/alz.71554.

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Susan's career focus has been on the development and protection of robust brands, and the research methodologies needed to support them. Much of her career has been spent consulting on the development of life science and technology commercialization strategy but she also has extensive experience with consumer products and financial services. She has contributed to the evolution of many standard research techniques, and she writes frequently on industry topics and issues of broader interest. In deference to changing times, the snappier-paced McDonald Minute replaces Susan's long-form SmartMouth blog, but with the same goal of connecting cultural themes to business challenges. She holds MA and PhD degrees from Annenberg School for Communication at the University of Pennsylvania.

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