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Preventing Alzheimer's Disease

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PERSPECTIVE

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Despite intensive laboratory and clinical research over three decades, an effective treatment to delay the onset and progression of Alzheimer's disease is not at hand. Recent clinical trial failures suggest that we must treat the disease earlier than in its mild to moderate stages, and major progress in validating presymptomatic biomarkers now makes secondary prevention trials possible. We will learn more about the natural history of the disease and any partial therapeutic responses from detailed analyses of recent trial results. This process will likely position the field for success, but only with much greater investment in all aspects of Alzheimer research and with careful design of future trials.

Few diagnoses in modern medicine evoke deeper apprehension in patient and family than Alzheimer's disease (AD). The implications of having cardiovascular disease, cancer, or metabolic disease are ominous, but surveys suggest that people particularly fear developing AD. This is so because Alzheimer's robs us of our most human qualities—reasoning, memory, abstraction, language, emotional control—and because a disease-modifying treatment remains beyond reach. This enormously common neurodegenerative disorder affects more than 5 million Americans and well over 35 million worldwide, numbers expected to grow dramatically as the population ages and competing causes of death in late life continue to recede (1). The projected rate of rise is even greater in the developing world than in the high-income countries (2) (Fig. 1).

As with other slowly progressive diseases, preventing AD depends on understanding early steps in its pathogenesis. A worldwide research effort during the past quarter century has yielded an increasingly detailed picture of the cytopathological, biochemical, and genetic underpinnings of the disease, including in its presymptomatic phase, and the parallel development of biomarker and neuroimaging modalities [reviewed in (3, 4)]. The classical lesions that Alois Alzheimer called attention to a century ago—extracellular amyloid plaques and intraneuronal neurofibrillary tangles—were shown in the mid-1980s to be composed, respectively, of the 42–amino acid β-amyloid protein (Aβ42) and the microtubule-associated protein tau. By the mid-1990s, decreased Aβ42 levels and increased tau levels in cerebrospinal fluid (CSF) were associated with a clinical diagnosis of AD (5). Soon, lowered CSF Aβ42 levels were documented in older people who appeared to have very early AD (sometimes referred to as mild cognitive impairment–amnestic type) or were still cognitively normal (6), with the rise in CSF tau levels generally following the Aβ42 decline (4). In the realm of neuroimaging, progressive hippocampal and cortical atrophy were measured with increasing precision before and during the clinical phase of AD, and this brain shrinkage was found to be accompanied by decreased cerebral metabolism on fluorodeoxyglucose positron emission tomography (FDG-PET). By 2004, the synthesis of a blood brain barrier penetrant, radiolabeled analog of the amyloid-binding dye thioflavin T [Pittsburgh compound B (PiB)], enabled researchers to image fibrillar amyloid deposits in vivo by PET (7). Taken together, these quantifiable markers of the evolving disease process in living human patients, now widely replicated in multiple studies (8), provide a critical resource for validating preventative and therapeutic agents in AD.

Pinpointing a Predisposition to AD

A small fraction (<1%) of all AD cases arises during middle age because of inherited missense mutations in one of three genes: APP, PSEN1, or PSEN2. The APP gene codes for the 695-amino-acid-long β-amyloid precursor protein (APP), which has salutary functions during brain development and in various biological processes in adulthood (9). All AD-causing mutations in APP alter amino acids within or immediately flanking its small ~42-residue Aβ region. The PSEN1 and PSEN2 genes code for two homologous (and redundant) intramembrane aspartyl proteases, presenilin 1 and presenilin 2 (10, 11). Therefore, all of these AD-causing mutations directly affect the biochemical reaction that generates Aβ42 and related peptides throughout life, by altering the substrate (APP) or the protease that cleaves this substrate (i.e., presenilin, the catalytic component of γ-secretase). The full penetrance of the mutations for early-onset, autosomal dominant AD and the fact that they result in a neuropathological, biochemical, and clinical phenotype largely indistinguishable from typical, late-onset ("sporadic") AD provide strong genetic evidence for the amyloid or Aβ hypothesis, which posits that AD arises in substantial part from a chronic imbalance between Aβ production and Aβ clearance in the brain. Numerous families carrying APP, PSEN1, or PSEN2 mutations have been studied collectively to determine the time course of fluid biomarker changes, neuroimaging changes, and clinical changes before the expected onset of AD symptoms, which is based on the age of symptom onset in a parent with the same mutation.

Initial analyses of a familial AD cohort [the Dominantly Inherited Alzheimer Network (DIAN)] suggest that Aβ42 levels in CSF begin to decline as early as 25 years before expected symptom onset (12). This is followed by the appearance of fibrillar amyloid deposits in the brain (as detected by PiB-PET), increased levels of tau in CSF, and progressive brain atrophy roughly 15 years before expected symptom onset (12). Cerebral hypometabolism and subtly impaired episodic verbal memory seem to begin some 10 years or so before expected symptoms (12). If this time course is generally similar to that of sporadic AD, and there is evidence from cross-sectional studies that it may be (4), then humans destined to develop AD have detectable biochemical and histopathological abnormalities two decades or more before overt clinical symptoms (Fig. 2).

Two key lessons that emerge from such studies of presymptomatic AD are that (i) profound brain alterations occur well before the dementia can be diagnosed (13) and (ii) therapeutic interventions directed only at the mild-to-moderate clinical stage may be too late to ameliorate symptoms. The latter conclusion is supported by recent phase 3 trials of certain Aβ-clearing monoclonal antibodies (e.g., bapineuzumab) that apparently failed to significantly slow cognitive and functional decline over 18 months, even though such antibodies are capable of preventing further rises in amyloid burden (14, 15) and lowering CSF phospho-tau levels, a key biomarker of AD-type neuronal degeneration (16).
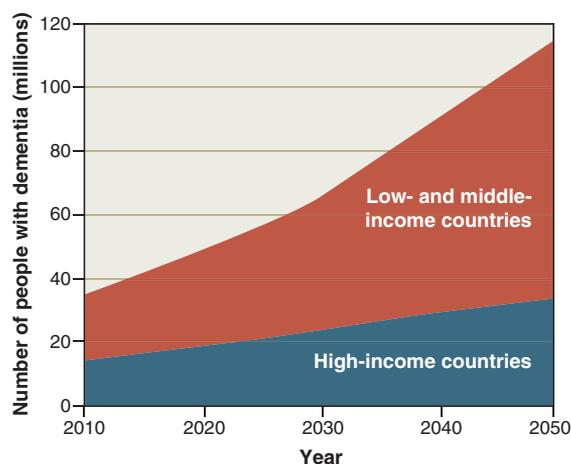

Fig. 1. Projected increases in the numbers of people with dementia in high-income countries and in low- and middle-income countries. [Figure reproduced, with permission, from (2)]

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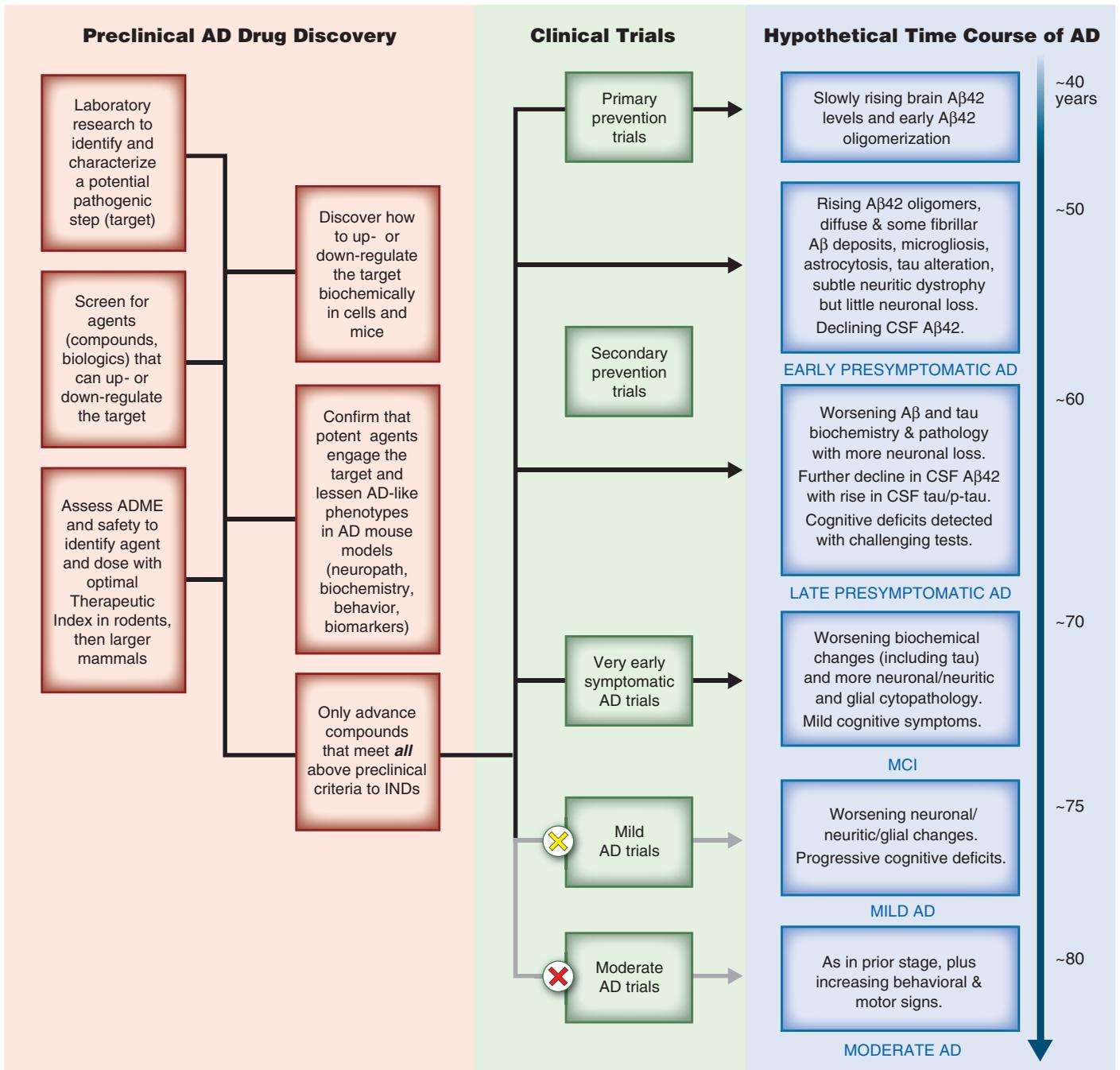
Preclinical AD Drug Discovery

Laboratory research to identify and characterize a potential pathogenic step (target)

Screen for agents (compounds, biologics) that can up- or down-regulate the target

Assess ADME and safety to identify agent and dose with optimal Therapeutic Index in rodents, then larger mammals

Discover how to up- or down-regulate the target biochemically in cells and mice

Confirm that potent agents engage the target and lessen AD-like phenotypes in AD mouse models (neuropath, biochemistry, behavior, biomarkers)

Only advance compounds that meet *all* above preclinical criteria to INDs

Clinical Trials

Primary prevention trials

Secondary prevention trials

Very early symptomatic AD trials

Mild AD trials

Moderate AD trials

Hypothetical Time Course of AD

Slowly rising brain Aβ42 levels and early Aβ42 oligomerization — ~40 years

Rising Aβ42 oligomers, diffuse & some fibrillar Aβ deposits, microgliosis, astrocytosis, tau alteration, subtle neuritic dystrophy but little neuronal loss. Declining CSF Aβ42. — ~50

EARLY PRESYMPTOMATIC AD

Worsening Aβ and tau biochemistry & pathology with more neuronal loss. Further decline in CSF Aβ42 with rise in CSF tau/p-tau. Cognitive deficits detected with challenging tests. — ~60

LATE PRESYMPTOMATIC AD

Worsening biochemical changes (including tau) and more neuronal/neuritic and glial cytopathology. Mild cognitive symptoms. — ~70

MCI

Worsening neuronal/neuritic/glial changes. Progressive cognitive deficits. — ~75

MILD AD

As in prior stage, plus increasing behavioral & motor signs. — ~80

MODERATE AD

Fig. 2. Aligning potential disease-modifying agents for AD with the course of the disease. Red boxes indicate the sequence of steps in the discovery of compounds or biologics as investigational new drugs (INDs) for AD. Blue boxes, speculative stages in the long presymptomatic and symptomatic phases of AD in a hypothetical individual who undergoes Aβ buildup for one of several possible reasons (e.g., a presenilin or APP mutation, ApoE4 inheritance, increased β-secretase activity, etc.) and develops very early symptoms by around age 70. Green boxes, clinical trial categories dependent on the stage of AD. Red X, trials in moderate AD not recommended. Yellow X, trials in mild AD recommended with caution. [Figure adapted from (35)]

Moving Toward Prevention Trials

Although antibodies against Aβ (anti-Aβ) that enhance clearance of the peptide and other Aβ-lowering agents, such as inhibitors of the β- and γ-secretase enzymes that generate Aβ, may still be shown to provide benefit in mildly symptomatic AD, the AD field has moved toward a consensus that secondary prevention (diagnosing and treating the disease before overt symptoms) is more likely to slow the pathogenic process (17–19) (Fig. 2). Such trials might be designed in the following way. Pre-symptomatic participants who bear deterministic mutations in *APP*, *PSEN1*, or *PSEN2* (i.e., auto-somal dominant AD) could undergo treatment with an Aβ-lowering or -neutralizing agent begin-ning 2 to 5 years or more before the expected age of onset of frank symptoms. In such trials, enrol-lees would have low CSF Aβ42 levels as well as brain amyloid deposits (detected by PET imaging) that exceed normal thresholds, ensuring that they can potentially respond to an anti-Aβ treatment.

Participants who do not yet have elevated CSF levels of tau or phosphorylated tau at trial entry could be compared with participants who already have these markers of tangle-associated neurodegeneration. Regarding outcomes, the treatment's capacity to delay the aforementioned biomarker changes [amyloid-PET and FDG-PET abnormalities; cerebral atrophy by volumetric magnetic resonance imaging (MRI); rising CSF levels of tau and phosphorylated tau] could be assessed yearly to ascertain the earliest point of deflection from the pathogenic trajectory of placebo-treated mutation carriers. Salutary movements of biomarkers would be expected to be seen first, but these might be accompanied by less decline on challenging cognitive tests that are sensitive to the cardinal manifestations of very early clinical AD (e.g., episodic memory loss and word learning and retrieval deficits) rather than more global cognitive tests [e.g., Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog), MiniMental State Examination (MMSE)] that have less sensitivity to detect early progression. Combined assessment of AD biomarker status and episodic memory should indicate whether the agent in question can slow disease progression over a 3- to 5-year interval. An academic consortium sponsored in part by the U.S. National Institutes of Health (NIH) and the biotechnology company Genentech has recently been approved to carry out such a secondary prevention trial with an anti-Aβ (crenezumab) in ~300 presymptomatic members of a large Colombian pedigree with the presenilin 1 Glu^{280}→Ala^{280} missense mutation and a smaller number of presymptomatic American participants from the DIAN cohort who carry other presenilin mutations (20). Another secondary prevention trial in autosomal dominant AD has been proposed to the NIH by the Alzheimer's Association and a consortium of DIAN sites and certain pharmaceutical companies (21).

In addition to conducting prevention trials in presymptomatic participants with rare, dominantly inherited AD, it is important to initiate similar studies as soon as possible in presymptomatic participants with common, late-onset AD (so-called sporadic AD). Here, it may be useful to divide participants by their apolipoprotein E genotypes, because the rate of AD pathogenesis and degree of β-amyloid burden are generally greater in patients with the E4 allele of this gene compared with those with just E3 or E2 alleles, and side effect profiles may differ. For example, phase 2 trials of bapineuzumab, a humanized monoclonal antibody to Aβ, indicated that ApoE4-positive participants were significantly more likely to develop an MRI change designated ARIA-E (amyloid-related imaging abnormality–edema or effusion; formerly called vasogenic edema) than were ApoE4-negative participants, presumably related to the heavier burden of microvascular amyloid in the former (22). Although only a small minority of participants treated with passive Aβ immunotherapy show ARIA-E on MRI, and most of these

experience no overt symptoms, subtle effects of this process on their mental status are possible and could partially mitigate any cognitive benefits of lowering and neutralizing Aβ. For some types of experimental anti-Aβ therapeutics, for example, the β- or γ-secretase inhibitors now under active development, prospective separation of trial participants by ApoE4 genotype may not be necessary, and stratification of the outcomes by genotype can be done at trial's end. A secondary prevention trial of an anti-Aβ in sporadic AD subjects (the A4 trial) is currently in advanced stages of planning by a consortium led by the Alzheimer's Disease Cooperative Study group funded by NIH (23).

Markers Before Mentation

As we move toward more optimal times for disease modification (i.e., very early symptomatic AD and secondary prevention before symptoms), the importance of obtaining CSF samples by lumbar puncture on as many trial participants as possible cannot be overstated. CSF provides a virtually ideal indicator of the biochemistry of the fundamental pathogenic processes of AD in vivo and in real time. The fact that multiple lengths of Aβ peptides (especially Aβ42, 40, and 38) and total and phosphorylated tau proteins can be quantified in small samples of CSF allows one to acquire simultaneous information about a putative pathogenic agent (Aβ) and a critical neuronal response molecule in AD (tau). Preclinical research shows that the expression of tau is necessary for Aβ peptides [including soluble oligomers that may contribute prominently to neuronal dysfunction (24)] to induce neuritic dystrophy and cytoskeletal collapse in cultured neurons (25) and behavioral deficits in APP transgenic mice (26). In the future, additional CSF analytes (e.g., other neuronal proteins, monocyte- and microglia-derived cytokines, certain lipids, metal ions, etc.) could provide a more sophisticated picture of the AD biochemical phenotype in vivo and also be used as biomarkers of progression.

The notion that lumbar puncture is uncomfortable and generally unacceptable to patients is badly out of date. Some investigators in Europe have been collecting CSF samples from participants with symptomatic and presymptomatic AD for many years, and clinicians in the United States need to catch up. The Alzheimer Disease Neuroimaging Imitative (ADNI; sponsored by the NIH and numerous biopharmaceutical companies) and some individual AD research centers have documented how feasible and informative routine CSF analysis can be [e.g., (27, 28)]. Patients and their families are usually amenable to lumbar puncture once they are informed of how important it is for accurate diagnosis and for assessment of trial outcomes, and the procedure can be quickly and safely performed in an outpatient setting (29). Ideally, each academic center or practice participating in AD trials should designate one or two highly

experienced physicians to perform all the lumbar punctures, as is done for other minimally invasive diagnostic procedures such as arthroscopy. Although the advent of PET amyloid imaging is a great boon to the presymptomatic diagnosis of AD, a low CSF level of Aβ42 is an equally if not more sensitive biomarker indicating that cerebral Aβ deposition is underway (28), and this information can be acquired at less expense than a PET scan.

Such considerations underscore the reality that we cannot validate efficacious disease-modifying agents in AD without strong reliance on biomarkers. The AD field often discusses the compelling example of blood lipid profiling in coronary artery disease (CAD), which led to regulatory approval of the first statin years before these low-density lipoprotein (LDL)–cholesterol–lowering drugs were unequivocally proven to prevent heart attacks (30). This achievement occurred because elevated cholesterol levels and abnormal lipoprotein profiles in blood had been tightly linked to the risk of progressive CAD by many epidemiological and mechanistic studies (31). The AD field is now approaching an analogous benchmark, with numerous CSF and neuroimaging studies consistently validating early changes in CSF Aβ42 and tau levels and cerebral amyloid deposition as indicative of a high risk of developing disease (8). It took years of clinical use of statins to be certain that therapeutically lowering LDL-cholesterol helped prevent morbidity and mortality in CAD (i.e., prove the cholesterol hypothesis) (30), and yet statin treatment was approved and rapidly expanded before that. Because neuropathological, genetic, mechanistic, biomarker, and even therapeutic research all support an early pathogenic role of Aβ42, the AD field needs to follow suit.

Although sensitive memory tests should always accompany biomarker assays in secondary prevention trials, rigorous and statistically significant outcomes on brain and CSF Aβ and tau should be considered for regulatory approval as long as an amyloid-lowering agent is deemed safe. Only with more widespread and prolonged use of a well-tolerated agent that hits AD biomarker endpoints can we ultimately determine whether the agent is efficacious on quality-of-life outcomes. Surveys indicate that many patients and their families are willing to undergo experimental testing of preventatives or early treatments, given the current absence of an approved disease-modifying therapeutic for this terrible, fatal disease. Approval of a safe agent that was designed on the basis of our current best understanding of AD mechanism should be considered on biomarker grounds alone, as has sometimes occurred in other chronic, life-threatening diseases.

Beyond Aβ

Why have agents targeting Aβ received so much therapeutic attention in AD? The principal reason is the wealth of evidence from many independent investigators worldwide supporting an early

role for Aβ dyshomeostasis in AD pathogenesis. Nonetheless, there remain appropriate concerns about Aβ as a cause and as a worthy therapeutic target in AD. Some of the considerable controversy that has swirled around this topic may represent misunderstandings of data and goals. I will describe just two key examples. First, there remains debate about whether Aβ accumulation is a cause or an effect of AD. Almost certainly, the answer is both. When APP or presenilins are mutant, Aβ overproduction appears to be the earliest identifiable molecular event associated with the development of AD. But in the vast majority of cases, an imbalance between Aβ production and clearance, which occurs in 100% of patients as we define AD, is caused by other upstream events, most currently unknown. One very important known cause is inheritance of one or two ε4 alleles of the apolipoprotein E gene (*32*). Such cases were once part of the broad swath of sporadic AD, but we now recognize ApoE4 as the single greatest risk factor for the disease besides age. Compelling evidence indicates that the ApoE4 protein decreases cellular clearance of Aβ and enhances the stability of extracellular Aβ aggregates in brain (*33*), but evidence for additional, non-Aβ–mediated effects, including on tau, is also accruing (*34*). Even though Aβ cannot be said to be solely causative in ApoE4 carriers (who may number at least half of AD cases), an agent that chronically reduces Aβ production (e.g., a β-secretase inhibitor or a γ-secretase modulator) or enhances its clearance (e.g., a passively administered Aβ antibody or an active Aβ vaccine) should be efficacious. In short, Aβ is both cause and effect in AD.

A second misunderstanding is the notion that therapies lowering Aβ could be dangerous because they would decrease the peptide's normal functions. Even years before symptomatic AD, brain levels of Aβ are very substantially increased, and no currently contemplated therapeutic would be expected to reduce them to subphysiological levels, just as therapeutic statin doses do not cause serum cholesterol to fall to dangerously low levels. Whether the Aβ fragment of APP acquired a biologically important function during evolution distinct from those of other proteolytic fragments of the precursor is under intensive study. For example, a recent report found that Aβ40 and Aβ42 peptides can favorably modify peripheral lymphoid and myeloid cell function to mitigate against experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis (*35*). But lowering the excessive brain levels of soluble Aβ peptides in AD to subphysiological levels is not contemplated and would be difficult to achieve.

These and other specific controversies surrounding the Aβ hypothesis have been discussed (*36*) and are widely viewed as not precluding further human research on Aβ-lowering strategies. At the same time, it is crucial to expend more preclinical and clinical research effort on non-Aβ strategies—for example, lowering excess levels

of tau proteins or down-regulating inflammatory cells both centrally and peripherally. Unfortunately, these approaches are well behind therapeutic development in the Aβ arena. We must substantially increase research on these alternative targets while also accelerating our judicious testing of Aβ-directed agents in presymptomatic or very early AD. Current research funding for AD is not nearly sufficient; it still represents a modest portion of the dollars our field needs to study AD comprehensively, and it is a very small fraction (<1%) of the enormous costs our society bears each year to provide care to AD patients.

Reducing AD Risk Without Drugs

Our understanding of environmental factors that modulate one's risk of developing AD lags behind our knowledge of the contributing genetic factors. Nonetheless, this important topic has been receiving increasing scrutiny. Lifestyle factors that may reduce the risk of dementia in general and AD in particular include physical exercise, cognitive activity and educational attainment, and social engagement. The protective effect of aerobic exercise (*37*, *38*) may derive from enhanced cardiovascular fitness and cerebrovascular health but possibly also from modifying the biology of AD, for example, by lowering Aβ accumulation or decreasing neuritic dystrophy. Lifelong intellectual activity and higher educational levels have been found to lessen the risk of developing AD or to ameliorate its course (*39*, *40*). In mouse models, environmental enrichment, including repeated exposure to novelty, has been shown to decrease amyloid burden and attendant neuroanatomical and behavioral deficits (*41*, *42*). Strong social engagement and lack of isolation in the elderly may contribute to a lower likelihood of developing dementia, including AD, or a slower progression of symptoms (*43*, *44*). Our current state of knowledge suggests that changes in lifestyle are unlikely to be sufficient to stave off the development of AD, particularly if these changes are instituted close to the time of clinical onset. However, it is possible that exposure to beneficial lifestyle factors over many years could delay the onset and progression of the disease. This research area merits rigorous investigation, given the ongoing challenges of validating a safe disease-modifying therapeutic and the high costs that will be incurred with its chronic administration.

Success from Failure

Attempts to treat complex, chronic diseases such as AIDS or certain forms of cancer have been marked by major failures before tangible success emerged. One hopes that this will be the case in AD. The appropriately intensive effort to test potential AD therapeutics earlier and in more carefully designed trials is likely to lead to rigorous scientific evidence of disease modification before long. This evidence may arise principally from biomarker data, although it will likely be accompanied by positive trends on cognitive tests. De-

spite being enormously disappointing to patients, families, and physicians, the field's recent clinical trial failures will provide a great deal of concrete information about what may work partially, what does not, and where to go next. As a society, we must invest much more and invest more wisely. We must broaden our therapeutic vision beyond Aβ and also move quickly to trials in very early symptomatic as well as presymptomatic participants. As soon as we see independently replicated evidence of relevant biomarker changes and some cognitive benefit, we should begin to consider even earlier ("primary") prevention trials for middle-aged participants bearing ApoE4 alleles. Our patients and their families should remind us of Churchill's exhortation: "…never, never, ever quit!"

References and Notes

1. R. Brookmeyer *et al.*, *Alzheimers Dement.* **7**, 61 (2011).
2. A. Wimo, M. Prince, *World Alzheimer Report 2010; the Global Economic Impact of Dementia* (Alzheimer's Disease International, London, 2010).
3. D. M. Holtzman, J. C. Morris, A. M. Goate, *Sci. Transl. Med.* **3**, 77sr1 (2011).
4. C. R. Jack Jr. *et al.*, *Lancet Neurol.* **9**, 119 (2010).
5. R. Motter *et al.*, *Ann. Neurol.* **38**, 643 (1995).
6. A. M. Fagan *et al.*, *Arch. Neurol.* **64**, 343 (2007).
7. W. E. Klunk *et al.*, *Ann. Neurol.* **55**, 306 (2004).
8. J. C. Morris, D. J. Selkoe, *Neurobiol. Aging* **32** (suppl. 1), S1 (2011).
9. U. C. Muller, H. Zheng, in *The Biology of Alzheimer's Disease*, D. J. Selkoe, E. Mandelkow, D. M. Holtzman, Eds. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2012), pp. 231–248.
10. C. Haass, D. J. Selkoe, *Nat. Rev. Mol. Cell Biol.* **8**, 101 (2007).
11. B. De Strooper, R. Vassar, T. Golde, *Nat Rev Neurol* **6**, 99 (2010).
12. R. J. Bateman *et al.*, *N. Engl. J. Med.* 120723122607004 (2012).
13. R. A. Sperling *et al.*, *Alzheimers Dement.* **7**, 280 (2011).
14. J. O. Rinne *et al.*, *Lancet Neurol.* **9**, 363 (2010).
15. S. Ostrowitzki *et al.*, *Arch. Neurol.* **69**, 198 (2012).
16. K. Blennow *et al.*, *Arch. Neurol.*, published online 4 May 2012.
17. T. E. Golde, L. S. Schneider, E. H. Koo, *Neuron* **69**, 203 (2011).
18. R. A. Sperling, C. R. Jack Jr., P. S. Aisen, *Sci. Transl. Med.* **3**, 111cm33 (2011).
19. R. J. Bateman *et al.*, *Alzheimers Res. Ther.* **3**, 1 (2011).
20. NIH Fogarty International Center, "First-ever Alzheimer's prevention trial to take place in Colombia" (2012), www.fic.nih.gov/News/Pages/2012-Alzheimer-prevention-trial-colombia.aspx.
21. Alzheimer Research Forum: News, "DIAN: What sayeth the regulator? Q&a with Rusty Katz," 15 May 2012, www.alzforum.org/new/detail.asp?id=3154.
22. R. Sperling *et al.*, *Lancet Neurol.* **11**, 241 (2012).
23. Alzheimer Research Forum: News, "Anti-amyloid treatment in asymptomatic ad trial," 27 December 2011, www.alzforum.org/new/detail.asp?id=3014.
24. D. M. Walsh, D. J. Selkoe, *J. Neurochem.* **101**, 1172 (2007).
25. M. Jin *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **108**, 5819 (2011).
26. E. D. Roberson *et al.*, *Science* **316**, 750 (2007).
27. L. M. Shaw *et al.*, *Ann. Neurol.* **65**, 403 (2009).
28. A. M. Fagan *et al.*, *Ann. Neurol.* **65**, 176 (2009).
29. N. Mattson *et al.*, *J. Alzheimers Dis.* **30**, 767 (2012).
30. D. E. Pankevich, T. Wizemann, B. M. Altevogt, *Alzheimer's Diagnostic Guideline Validation: Exploration of Next Steps: Workshop Summary* [Institutes of Medicine (IOM), National Academies Press, Washington, DC, 2012].
31. M. S. Brown, J. L. Goldstein, *Science* **272**, 629 (1996).
32. E. H. Corder *et al.*, *Science* **261**, 921 (1993).
33. J. M. Castellano *et al.*, *Sci. Transl. Med.* **3**, 89ra57 (2011).
34. R. W. Mahley, Y. Huang, *Ann. Neurol.* **65**, 623 (2009).
35. J. L. Grant *et al.*, *Sci. Transl. Med.* **4**, 145ra105 (2012).

36. D. J. Selkoe, *Nat. Med.* **17**, 1060 (2011).
37. N. T. Lautenschlager *et al.*, *JAMA* **300**, 1027 (2008).
38. K. A. Intlekofer, C. W. Cotman, *Neurobiol. Dis.*, published online 4 July 2012); .
39. C. Sattler, P. Toro, P. Schönknecht, J. Schröder, *Psychiatry Res.* **196**, 90 (2012).
40. S. M. Landau *et al.*, *Arch. Neurol.* (2012).
41. S. A. Wolf *et al.*, *Biol. Psychiatry* **60**, 1314 (2006).
42. D. A. Costa *et al.*, *Neurobiol. Aging* **28**, 831 (2007).
43. H. X. Wang, A. Karp, B. Winblad, L. Fratiglioni, *Am. J. Epidemiol.* **155**, 1081 (2002).
44. J. Verghese *et al.*, *Neurology* **66**, 821 (2006).

PERSPECTIVE

Changing Human Behavior to Prevent Disease: The Importance of Targeting Automatic Processes

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Much of the global burden of disease is associated with behaviors—overeating, smoking, excessive alcohol consumption, and physical inactivity—that people recognize as health-harming and yet continue to engage in, even when undesired consequences emerge. To date, interventions aimed at changing such behaviors have largely encouraged people to reflect on their behaviors. These approaches are often ineffectual, which is in keeping with the observation that much human behavior is automatic, cued by environmental stimuli, resulting in actions that are largely unaccompanied by conscious reflection. We propose that interventions targeting these automatic bases of behaviors may be more effective. We discuss specific interventions and suggest ways to determine whether and how interventions that target automatic processes can enhance global efforts to prevent disease.

At the 65th World Health Assembly held in Geneva in May 2012, health ministers pledged a 25% cut in premature deaths from the four most prevalent noncommunicable diseases—diabetes, cardiovascular disease, lung disease, and cancer—by 2025. Achieving this will require sizeable shifts in the population distribution of consumption of calories, tobacco, and alcohol, as well as increased levels of physical activity and fruit and vegetable consumption. But how might such changes in behavior be achieved? Hitherto, nonregulatory approaches to changing behaviors across individuals and populations have focused largely on using information to persuade people of the risks they face and the potential benefits of change, through clinics or public health campaigns, such as those aimed at increasing the consumption of fruit and vegetables or at reducing the consumption of alcohol. More recent variants of this approach include personalizing risk messages using the results of a wide array of biomarker tests, including blood glucose levels indicating an increased risk of diabetes and gene variants indicating an increased risk of heart disease. These approaches have had either modest or no effects on health-harming behaviors (*1, 2*).

We propose that the potential for information-based interventions is fundamentally limited, given that it is based on a view of human behavior that is at odds with psychological and neuroscientific evidence that much human behavior is not actually driven by deliberation upon the consequences of actions, but is automatic, cued by stimuli in the environment, resulting in actions unaccompanied by conscious reflection (*3*).

Flexibility Versus Efficiency: Understanding the Balance in Human Behavior

Throughout our day, we shift between two broad categories of behavior (*4, 5*). On the one hand, we may act in a reflective manner, directing ourselves toward particular goals, aware of our motivations and actions and able to halt or modify them should the need arise. In other instances, we act without reflection, responding to our surroundings in complex ways while our thoughts may be far removed. Each of these types of behavior has its advantages and disadvantages. The former is goal-directed, flexible, and rational insofar as it is motivated by explicit beliefs and desires. But it is also slow, cumbersome, and metabolically costly, absorbing our attention and preventing other processing. It is especially inefficient when it comes to routine situations: Why would one wish to deliberate over each stage of a familiar route home? The latter behaviors, in their automaticity, have the advantage of capitalizing on the routine and the predictable, freeing us to devote our cognitive capacity to other matters while nevertheless engaging in complex and fruitful actions. However, in becoming divorced from awareness and reflection, these automatic behaviors lose flexibility and may become out of touch with conscious desires, proceeding even when the consequences are unwanted. Thus, we may find ourselves taking the well-travelled route home when the original intention had been to call elsewhere.

Although it is usual to draw a complete distinction between these two broad categories of behavior, in fact they overlap and interact, with any given behavior consisting of a complex mixture of the two. Ideally, they would, and often do, complement each other, but they may also come into conflict. This is particularly so in the case of health-related behaviors, for which people often have competing goals (such as a pleasure goal of enjoying a cake versus a health goal of reducing weight). It is perhaps most useful to think of them in terms of a balance, with certain factors promoting the more reflective and others the more automatic behaviors. Thus, for example, engaging in a task that absorbs attention may shift us toward more automatic behavior. This is illustrated in an experiment showing that having to remember a long string of numbers made people more likely to select chocolate cake than fruit salad when presented with a forced choice in the middle of the experiment (*6*). Stress too can shift us from being rational and goal-directed to more automatic, responding to external stimuli and persisting in actions that are not ultimately helpful.

The above distinction is very relevant to established experimental work on habits, which are actions that occur in response to stimuli without necessarily bringing to mind the goal of that action. Habits are contrasted with goal-directed behavior and form one class of automatic behavior. They become established by repetition and routine, their emergence being marked by measurable changes in brain circuits (*7*). Although habits constitute an important class of automatic behavior, it is important to note that not all automatic behavior is habitual. For example, viewing a beer advertisement on television may result in the viewer going to the fridge for a beer without awareness of the

> "**N**inety-nine hundredths or, possibly, nine hundred and ninety-nine thousandths of our activity is purely automatic and habitual, from our rising in the morning to our lying down each night."
>
> **William James (1899)**

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