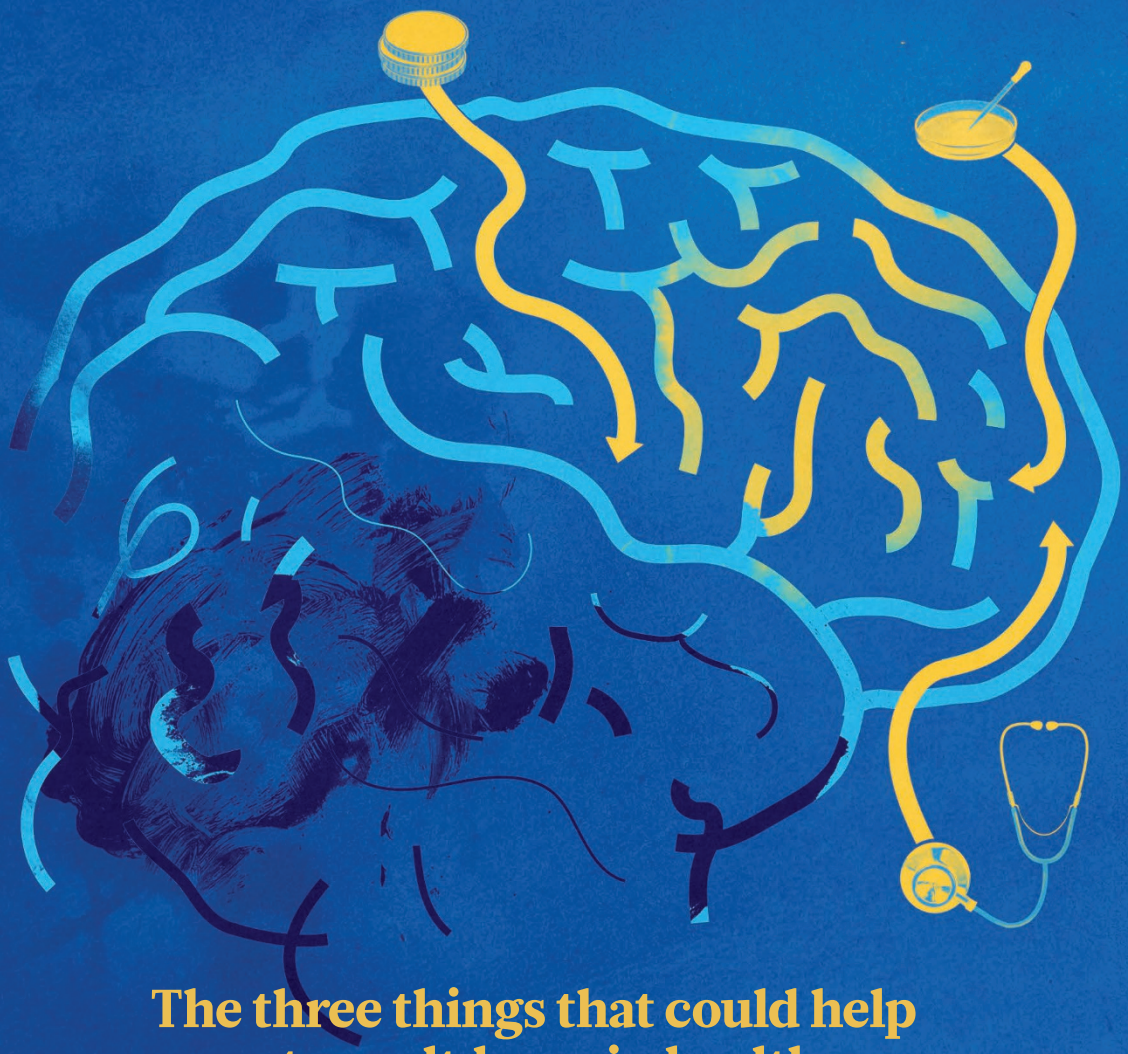
HOW TO DEFEAT DEMENTIA



The three things that could help prevent a meltdown in health-care systems worldwide.

BY ELIE DOLGIN

There are not a lot of things that could bring together people as far apart on the US political spectrum as Republican Newt Gingrich and Democrat Bob Kerrey. But in 2007, after leading a three-year commission that looked into the costs of care for elderly people, the political rivals came to full agreement on a common enemy: dementia.

At the time, there were fewer than 30 million people worldwide diagnosed with the condition, but it was clear that the numbers were set to explode. By 2050, current predictions suggest, it could reach more than 130 million, at which point the cost to US health care alone from diseases such as Alzheimer's will probably hit US$1 trillion per year in today's dollars. "We looked at each other and said, 'You know, if we don't get a grip on Alzheimer's, we can't get anything done because it's going to drown the system,'" recalls Gingrich, the former speaker of the US House of Representatives.

He still feels that sense of urgency, and for good reason. Funding has not kept pace with the scale of the problem; targets for treatments

are thin on the ground and poorly understood; and more than 200 clinical trials for Alzheimer's therapies have been terminated because the treatments were ineffective. Of the few treatments available, none addresses the underlying disease process. "We're faced with a tsunami and we're trying to deal with it with a bucket," says Gingrich.

But this message has begun to reverberate around the world, which gives hope to the clinicians and scientists. Experts say that the coming wave can be calmed with the help of just three things: more money for research, better diagnostics and drugs, and a victory — however small — that would boost morale.

"What we really need is a success," says Ronald Petersen, a neurologist at Mayo Clinic in Rochester, Minnesota. After so many failures, one clinical win "would galvanize people's interest that this isn't a hopeless disorder".

COST CALCULATIONS

Dementia is the fifth-biggest cause of death in high-income countries, but it is the most expensive disease to manage because patients require constant, costly care for years. And yet, research funding for dementia pales in comparison with that for many other diseases. At the US National Institutes of Health (NIH), for example, annual funding for dementia in 2015 was only around $700 million, compared with some $2 billion for cardiovascular disease and more than $5 billion for cancer.

One problem is visibility. Other disease communities — most notably, people affected by breast cancer and HIV/AIDS — have successfully advocated for large pots of dedicated research funding. But "there simply wasn't any comparable upswell of attention to Alzheimer's", says George Vradenburg, chair and co-founder of UsAgainstAlzheimer's, a non-profit organization in Chevy Chase, Maryland.

The biggest reason, he says, is that "the victims of the disease hide out". Dementia mostly affects elderly people and is often misconstrued as a normal part of ageing; there is a stigma attached to the condition, and family care-givers are often overworked and exhausted. Few are motivated enough to speak up.

However, social and political awareness has increased in the past five years. "We all started to work together a lot more, and that helps," says Susan Peschin, chief executive at the Alliance for Aging Research in Washington DC, one of more than 50 non-profit groups in the Accelerate Cure/Treatments for Alzheimer's Disease coalition.

The impact can be seen in government investments. France took action first, creating a national plan for Alzheimer's in 2008 that included €200 million (US$220 million) over five years for research. In 2009, the German Centre for Neurodegenerative Diseases in Bonn was created with a €66-million annual budget. And UK spending on dementia research more than doubled between 2010 and 2015, to £66 million (US$82 million). The European Union has been dishing out tens of millions of euros each year for dementia studies through the Innovative Medicines Initiative and the Joint Programming process, and Australia is now about halfway through doling out its Aus$200-million (US$150-million), five-year dementia-research fund.

"This is a global challenge, and no one country will be able to solve the problem," says Philippe Amouyel, a neurologist and geneticist at the University Hospital of Lille in France. Yet it's the United States that has been the biggest backer by far, thanks in part to efforts by Gingrich and Kerrey. The NIH's annual budget for Alzheimer's and other dementias jumped in the past year to around $1 billion, and there is support for a target to double that figure in the next few years — even in the fractious US political landscape. "Alzheimer's doesn't care what political party you're in," says Kerrey.

> "WE'RE FACED WITH A TSUNAMI AND WE'RE TRYING TO DEAL WITH IT WITH A BUCKET."

Two billion dollars is "a reasonable number", says Petersen, who chairs the federal advisory board that came up with the target in 2012. Now, he adds, the research community just needs to work out "what are we going to do with it if in fact we get it?".

The answer could depend in large part on the fate of a drug called solanezumab, developed by Eli Lilly of Indianapolis, Indiana. This antibody-based treatment removes the protein amyloid-β, which clumps together to form sticky plaques in the brains of people with Alzheimer's. By the end of this year, Lilly is expected to announce the results of a 2,100-person clinical trial testing whether the drug can slow cognitive decline in people with mild Alzheimer's. It showed preliminary signs of cognitive benefit in this patient population in earlier trials (R. S. Doody *et al. N. Engl. J. Med.* **370,** 311–321; 2014), but the benefits could disappear in this final stage of testing, as has happened for practically every other promising compound.

No one is expecting a cure. If solanezumab does delay brain degradation, at best it might help people to perform 30–40% better on cognitive tests than those on a placebo. But even such a marginal gain would be a triumph. It would show scientists and the drug industry that a disease-modifying therapy is at least possible. By contrast, another setback could bring recent momentum in therapeutic development to a halt.

"This is a fork in the road," says John Hardy, a neurogeneticist at University College London. "This is going to be a very important outcome, way beyond the importance for Lilly and this particular drug."

On a scientific level, success for solanezumab could lend credence to the much-debated amyloid hypothesis, which posits that the build-up of amyloid-β in the brain is one of the triggers of Alzheimer's disease. The previous failure of amyloid-clearing agents led many to conclude that plaques were a consequence of a process in the disease, rather than the cause of it. But those in favour of the amyloid hypothesis say that the failed drugs were given too late, or to people with no amyloid build-up — possibly those with a different form of dementia.

For its latest solanezumab trial, Lilly sought out participants with mild cognitive impairment, and used brain scans and spinal-fluid analyses to confirm the presence of amyloid-β in their brains. Another company, Biogen in Cambridge, Massachusetts, took the same approach to screening participants in a trial of its amyloid-targeting drug aducanumab. Earlier this year, a 165-person study reported early signs that successfully clearing amyloid-β with the Biogen therapy correlated with slower cognitive decline (J. Sevigny *et al. Nature* **537,** 50–56; 2016).

If those results hold up to further scrutiny, "that will at least tell us that amyloid is sufficiently upstream in the cascade that it deserves being targeted and tackled pharmacologically", says Giovanni Frisoni, a clinical neuroscientist at the University of Geneva in Switzerland who is involved in the drug's testing.

TO DEFEAT, DELAY

Although debate over the amyloid hypothesis continues, interest is growing in earlier intervention with drugs that clear the protein. Reisa Sperling, a neurologist at Brigham and Women's Hospital in Boston, Massachusetts, worries that even mild dementia is a sign of irreparable brain-cell death. "You can suck all the amyloid out of the brain or stop it from further accumulating, but you're not going to grow those neurons back."

That is why she is leading Anti-Amyloid Treatment in Asymptomatic Alzheimer's, or A4, a $140-million, placebo-controlled solanezumab study that aims to treat people with elevated amyloid levels before they show any signs of cognitive impairment. And A4 is not her only trial. In March, she and neurologist Paul Aisen of the University of Southern California's Alzheimer's Therapeutic Research Institute in San Diego launched a trial in 1,650 asymptomatic people with early signs of amyloid-β build-up. It will test a pill from Johnson & Johnson that blocks β-secretase, an enzyme responsible for producing the toxic protein.

These interventions are known as secondary prevention because they target people who are already developing amyloid plaques. Sperling and Aisen also plan to test what's

ILLUSTRATION BY ANDY POTTS

called primary prevention. In August, they received NIH funding to start treating people who have normal brain levels of amyloid-β and no signs of cognitive decline, but who have a high risk of developing Alzheimer's — because of a combination of factors such as age and genetics.

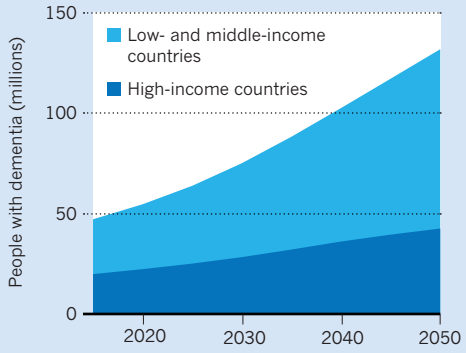
"The biggest impact we can have is in delaying the onset of the diseases," says David Holtzman, a neurologist at Washington University School of Medicine in St. Louis, Missouri, and an investigator in the Dominantly Inherited Alzheimer Network, which is testing the benefits of giving either solanezumab or another anti-amyloid therapy to people who inherit gene mutations that predispose them to develop Alzheimer's at an early age.

Secondary prevention could eventually mean screening everyone past middle age for signs of amyloid-β, although the current testing methods are either expensive ($3,000 brain scans) or invasive (spinal taps). Researchers have flagged a dozen possible blood-based biomarkers, but none has yet panned out, says Dennis Selkoe, a Brigham and Women's Hospital neurologist.

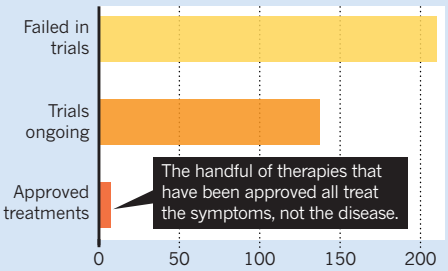
Yet a cheap and easy diagnostic test for amyloid-β could ultimately prove unnecessary. In the same way that some have suggested giving cholesterol-lowering drugs to anyone at risk of heart disease, clinicians might eventually give anti-amyloid drugs to a broad set of people prone to Alzheimer's — even if they are not already amyloid positive, says Sperling.

THE APPROACHING WAVE

The number of people living with dementia worldwide will more than double in the next 35 years. Low- and middle-income countries will be the hardest hit.



Hundreds of clinical trials for Alzheimer's disease have been terminated because the treatments were ineffective.



SOURCE: TOP, ALZHEIMER'S DISEASE INTERNATL GO.NATURE.COM/2EIJ1BW; BOTTOM, B. MUNOS

TARGET PRACTICE

Just as cholesterol is not the sole cause of heart disease, amyloid-β is not the only driver of Alzheimer's. There's also tau, a protein that causes tangles in the brains of most people with Alzheimer's. Several pharmaceutical companies are targeting tau, but few large drug-makers have clinical candidates directed at other types of target. "They know how to modulate a specific target and keep looking under that lamp post, rather than venturing away from their comfort zones," says Bernard Munos, an industry consultant and former Eli Lilly executive.

That's a problem, says Howard Fillit, chief science officer of the Alzheimer's Drug Discovery Foundation in New York City. "We really need to increase the diversity of targets we're tackling."

After amyloid and tau, the only target receiving much attention from researchers is neuroinflammation — the "third leg of the stool" in treating Alzheimer's, according to neurogeneticist Rudy Tanzi at Massachusetts General Hospital in Boston.

He likens Alzheimer's disease to a wildfire in the brain. Plaques and tangles provide the initial brush fires, but it's the accompanying neuroinflammation that fans the flames. Once the blaze is raging, Tanzi says, "putting out those brush fires that got you there isn't good enough".

This could explain why anti-amyloid drugs failed when given to people with full-blown dementia. For these individuals, perhaps reducing the inflammatory activity of brain immune cells called microglia could help. Drug researchers are now focusing on two genes, *CD33* and *TREM2*, that are involved in microglial function. But, says Tanzi, "there are two dozen other genes that deserve attention. Who knows if one of these new genes that no one is working on might lead to drug clues?"

ALTERNATIVE AVENUES

Many Alzheimer's experts emphasize the need to develop better low-cost interventions that don't require drug research. At the University of New South Wales in Sydney, Australia, for example, geriatric psychiatrist Henry Brodaty is testing whether an Internet coaching tool that focuses on diet, exercise, cognitive training and mood can postpone disease development. "We know that two-thirds of the world's dementia is going to be in developing countries," he says (see 'The approaching wave'). Lifestyle interventions, he argues, could be more broadly scalable than expensive drugs.

Researchers also need to look beyond Alzheimer's, to the many other types of dementia. Injuries to the vessels that supply blood to the brain cause a form called vascular dementia. Clumps of a protein called α-synuclein underlie cognitive problems in people with Parkinson's disease and also what's called Lewy body dementia. Tau deposits are often behind the nerve-cell loss responsible for frontotemporal dementia. And there are many other, equally devastating, drivers of serious mental decline.

"We should not be ignoring these other diseases," says Nick Fox, a neurologist at University College London, especially given that many types of dementia share biological mechanisms. Tackling one disease could help inform treatment strategies for another.

But perhaps the biggest hindrance to drug development today is more logistical than scientific, with clinical trials for dementia taking years to complete as investigators struggle to recruit sufficient numbers of study participants. "We need to get answers more quickly," says Marilyn Albert, director of the Johns Hopkins Alzheimer's Disease Research Center in Baltimore, Maryland.

One solution is trial-ready registries. By enrolling people who are interested in taking part in a study before it actually exists, investigators can start a trial as soon as a drug comes along for testing. "We have to register humanity in the task of defeating this disease," says Aisen.

The 1,600-person COMPASS-ND registry is being funded through the Canadian Consortium on Neurodegeneration in Aging. Member Serge Gauthier, a neurologist at McGill University in Montreal, says that finding participants can be challenging. But he adds that around one-third of the people who come to memory clinics such as his have what's known as subjective cognitive impairment — they might forget names or suffer from other 'senior moments', but they do not meet the clinical definition of dementia.

They are perfect for trial-ready registries, says Gauthier: they are at an elevated risk of the disease, and they've demonstrated concern. Gauthier wants to find more people like them. He fits the profile himself, so he joined the Brain Health Registry, which has more than 40,000 participants so far and is led by researchers at the University of California, San Francisco. He takes regular cognitive tests, and could be asked to do more once potential diagnostic tools or therapies are ready for testing. "It's a fun thing to do," he says.

Voluntarily or not, people will need to face up to dementia, because in just a few short decades, pretty much everyone is going to have a friend or loved one affected by the disease. It's an alarming idea, and it should spur action, says Robert Egge, chief public policy officer of the Alzheimer's Association in Chicago, Illinois.

"We know where we're heading," he says. "The question is: are we going to get in front of it or not?" ■ SEE BOOKS & ARTS P.166

Elie Dolgin *is a science writer in Somerville, Massachusetts.*