Century-long war on Alzheimer's edges towards uncertain endgame

THE TIMES
THE AGE OF DEMENTIA

A cure has proved elusive but there is cause for optimism, **Oliver Moody** writes

In 1901 a 51-year-old woman called Auguste Deter sat down to a lunch of pork and cauliflower in the Frankfurt lunatic asylum.

"What are you eating?" her new doctor asked. "Spinach," she said, ferrying another forkful of meat into her mouth. "What are you eating now?" "First I eat the potatoes. Then the horseradish."

She was dead within five years. Some of the sharpest minds in medical science have spent more than a century pursuing a cure for the nightmarish disease that Alois Alzheimer encountered that day. Pharmaceutical firms have poured tens of billions of pounds into their efforts to crack the formula for what would be one of the most profitable drugs in history.

To date, all have failed. Why? And what happens now? It is three years since the governments of the G8 nations, Britain among them, promised to end the wait for a cure or therapy by 2025.

The good news is that with more than 50 new therapies being tested on patients there is guarded optimism among scientists that the promise can be kept. The bad news is that when, or if, such a drug is developed, it is likely to be too little, and much too late, for most of the one million Britons who are expected to have been diagnosed with dementia by that point.

Researchers are coming to regard Alzheimer's disease, by far the most common of the dementias, as a much more devious enemy than the textbooks let on, particularly among the elderly patients who make up three quarters of its victims.

In its essentials, the battle plan has not been radically redrawn since Mrs Deter's death in 1906. When Alzheimer examined little stained slices of her brain under a microscope, he saw that the cells were literally bursting with strange lumps and sticky tangles.

Today we call the poisonous proteins amyloid beta and tau, and they are regarded by drugs companies as the Osama bin Laden of dementia. Clean out this sticky poison, the logic goes, and you clean out the disorder.

Yet this logic is looking ever more inadequate. Last year two of the most promising weapons against the amyloid-tau axis of evil, LMTX and solanezumab, failed at the last stage of their human trials. The new frontrunners are aducanumab, a kind of molecular beacon that is supposed to latch on to the amyloid clumps and remove them, and a fleet of molecules called BACE1 inhibitors, which block a precursor to the amyloid and should in theory stop it from forming in the first place.

Once again the omens look good. Aducanumab has gone into a big clinical trial after it was found to nobble amyloid and possibly even halt patients' cognitive decline in its first round of tests. Experts are even more excited about the BACE1 inhibitors such as Merck's verubecestat, which may well "turn off the tap" of Alzheimer's. Its first crop of end-stage results is expected in July.

In this game, however, disappointment is an occupational hazard. Researchers are increasingly questioning whether any single drug can fight advanced Alzheimer's on its own.

"I'm a type 2 diabetic and I take three different drugs," John Hardy, professor of neuroscience at University College London, said. "And this is where we are heading with Alzheimer's. Having one drug would be excellent, but the eventual position we will end up with is polypharmacy."

Few serious scientists deny that amyloid and tau are part of the disease but they are no longer thought to be the whole story. Just as important seems to be the health of the intricate canal network of vessels that feed blood to the brain and carry its rubbish away. Evidence suggests the breakdown of this system may precede the classic physical ravages of Alzheimer's.

Roy Weller, emeritus professor of medicine at the University of Southampton, believes drugs that unclog the arterial drains will be tough to design but could prove invaluable. Others have found signs that the chronic hyper-belligerence of the cerebral immune system is a third front in the war on dementia.

Julie Williams and her team at Cardiff University have identified more than two dozen genes that hold the blueprints for different parts of the brain's defences against disease. Their theory is that Alzheimer's is as much the result of these safety mechanisms going haywire as of any protein — and this insight could open a new war chest of potential treatments. "I'm very hopeful that some of these therapies could be achievable within five to ten years," Professor Williams said. "We now have a very firm body of evidence pointing towards a number of mechanisms."

Rita Guerreiro, of UCL, was named Alzheimer's Research UK's young investigator of the year for her discovery that another immune system gene, TREM2, appears to be one of the most important culprits. When this goes wrong it seems to take the brakes off immune cells. The brain effectively tears itself apart in a slash-and-burn defence that may be more damaging than the threat it is supposed to suppress. Dr Guerreiro thinks we may soon see drugs that can calm down this wild overreaction and spare patients the worst ravages of the condition.

It seems likely that what we call Alzheimer's is really the wreckage caused by these three processes — the amyloid "cascade", the breakdown of the blood supply, and the berserk immune system — as they lash each other into a mutual frenzy. If this is true, then each arm of the disease could well need at least one class of drugs to itself.

There are other, more swashbuckling, approaches out there. A group led by Gary Lynch at the University of California, Irvine, thinks that ampakines, another family of drugs that encourage brain cells to change their signalling routes, may help people to fight back, not only against dementia but against the cognitive ageing process itself.

He said: "We recently obtained remarkable results in middle-aged rats. There is growing evidence from animals and humans for brain atrophy as part of normal ageing; our results reversed much of this."

There is no shortage of ideas, nor of miraculously cured rats. What patients urgently need is tangible human results. And in this respect — ultimately, the only respect that really matters — Auguste Deter would have been little better off today than she was in 1901.

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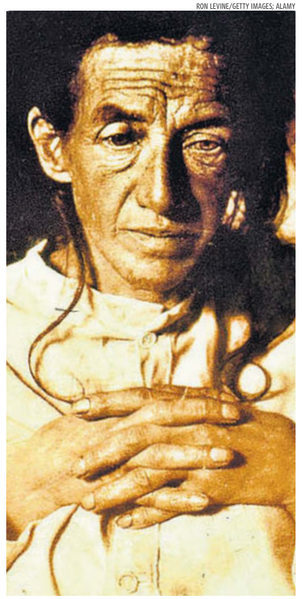
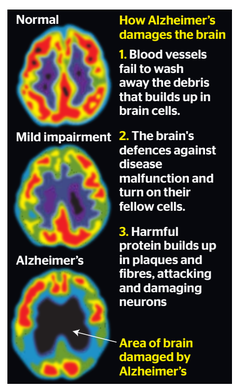
RON LEVINE/GETTY IMAGES; ALAMY



Billions of pounds have been spent on research into dementia but little has changed for patients since Auguste Deter's condition was identified by Alois Alzheimer, below, more than 100 years ago



How mice immunity is hindering research

Tom Whipple Science Editor

Mice do not get dementia. This is particularly ironic because we are especially good at curing it in them.

In laboratories across the world mice are genetically engineered to deposit amyloid in the brain, as happens in humans with Alzheimer's, and then given drugs that make them better. Then those drugs are tested on humans and, at least so far, nothing happens.

Some scientists increasingly believe that one of the reasons Alzheimer's research appears to have stalled is that the entire discipline is based on shaky, rodent foundations.

"The big problem of mouse models of Alzheimer's is that amyloid deposition is not part of the biology of mice," George Perry, from the University of Texas at San Antonio, said. "You're creating a problem that doesn't exist in that mouse at all. You create the problem, you remove the problem."

He likened it to simulating respiratory problems by putting a plastic bag on someone's head. "It's easy to cure — you take the plastic bag off the head. But what have you really done?"

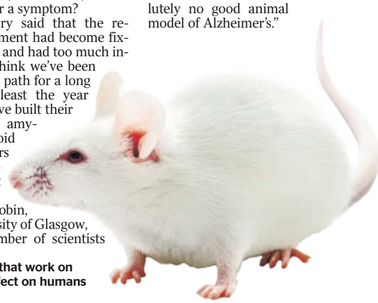
Mice are a mainstay of scientific research. In drug discovery they are the first step in testing compounds that will save lives. Everyone accepts that what works in a mouse may not work, or may not be safe, in a human. The difference with Alzheimer's is that we do not know enough about the disease even to be sure that the mice engineered to have it, have it. Is amyloid, for instance, a cause of Alzheimer's or a symptom?

Professor Perry said that the research establishment had become fixated on amyloid and had too much invested in it. "I think we've been down the wrong path for a long time, since at least the year 2000. People have built their careers around amyloid. If amyloid falls, their careers fall. Do you expect them to let go?"

Andrew Tobin, from the University of Glasgow, is one of a number of scientists taking a different approach. "We do malaria research. We give a mouse malaria, it gets malaria, and we cure it. That is simple. This, neurodegeneration, is a very different ball game.

"None of the Alzheimer's models give you progressive terminal neurodegeneration. There is synaptic loss, true. There is a build-up of amyloid plaques, true. But the disease doesn't take the form of that you would expect in an Alzheimer's patient. That mouse doesn't die of neurodegeneration."

For a recent piece of research, in which he and his colleagues reversed memory loss in mice, he avoided conventional mouse models entirely. Instead they treated mice with a form of prion disease — similar to CJD, the human variant of mad cow disease.



Dementia cures that work on mice have no effect on humans

TOMORROW
The race to protect healthy brains against dementia

The condition was very different from Alzheimer's but it was, at least, something that caused progressive neurodegeneration and death.

Professor Tobin said that mouse research was crucial. "Without formulating hypotheses in mice, albeit imperfect, I don't see how any progress could be made," he said.

But, equally, he described it as a significant reason why dementia posed such a major research problem. "You cannot avoid the fact that there is absolutely no good animal model of Alzheimer's."

VIDEO
Diagnosed with dementia at 58: a case study
On mobile, tablet and at thetimes.co.uk

Extra help for confused customers

Tom Whipple

Even if a customer seems cognitively normal, British Gas technicians are trained to spot subtle signs that they may have dementia. For instance, "people with dementia often leave loads of notes on the fridge," said Steve Crabb, head of vulnerable customers at British Gas.

Heathrow staff are also trained to spot customers with dementia, but here the signs are different. Jonathan Coen, director of customer relations, said they keep an eye out for people who are disoriented, so they can offer assistance. "What we are finding is most passengers want to be able to travel independently, they just need extra help at security and arrivals. But if necessary we will look after people through the whole journey, through security, on to the aircraft," he said.

Businesses are increasingly preparing for a future in which dealing with customers with dementia is common. There are pragmatic reasons for it — in five years a million people in Britain will have dementia, and most patient groups and charities believe they will be spending longer living in society.

For British Gas that means knowing when to be more patient with people, but it also means making practical adaptations. The company is making it easier for relatives to have access to smart thermostats, to check the temperature. It has also completely overhauled the system for dealing with power of attorney.

"Previously our process was very cumbersome, you would send documents to a PO Box in Rotherham, to be answered somewhere else, and uploaded somewhere else again," said Mr Crabb. "We made it simpler, and easier. It's probably saving us money as well."

At Heathrow, concerns are different. There is no long-term relationship with customers. Instead, they are slowly training the workforce to understand how to deal with people with dementia. The next step is making security staff aware, so that even if people have not opted to be guided through the airport they can still be helped at critical points.

"They might be fine elsewhere, but just need help preparing the right documentation or understanding the liquid requirements," said Mr Coen.

Although, admittedly, the same might go for most other customers as well.