Carol Jennings was the teacher from Coventry behind a breakthrough in Alzheimer's. The tragedy is that by the time that discovery came, she had no idea. She had the disease too

When her father and four of his siblings were diagnosed with Alzheimer's, Carol Jennings thought there must be a link. Thanks to her, a protein that drives the disease was identified. Is it the beginning of the end of this form of dementia? Tom Whipple finds out

Stuart and Carol Jennings photographed at home in Coventry last year by Jay Brooks

For the rest of her life Carol Jennings kept a copy of the letter she sent, the most important letter in dementia research.

It is June 2023. I am sitting beside her in her front room. Facing a mantelpiece of photographs that chronicle the 40 years of life that came after the letter, I unfold and read it.

"I was very interested to read of your research in the Alzheimer's Disease Society News and think my family could be of use," it begins, written in the careful, neat handwriting of a teacher.

Her father, Walter, then 63, had Alzheimer's, she told the scientists. So did his younger sister, Audrey. "His brother Arthur also may have the disease," she speculated and would later be proved correct. Her grandfather, she suspected, had died of it. Enclosed was a family tree.

Alzheimer's, according to the orthodoxy of the time, did not run in families. If that was so, how to explain her family? "Please contact me," she continued, "if you think we should be of help."

It certainly was. In 1991, five years after that letter was sent, The Times published an article about the findings, headlined "Family link leads to breakthrough on Alzheimer's disease". Beside it was a picture of Carol and her two children, Emily and John.

Last year the newspaper published another piece. This time it was on the front page: "Drug raises hope of ending Alzheimer's".

There was no mention of the Jennings family in that article. Amid the topline results of a phase three clinical trial, merely the latest to show – after years with no progress – that we can alter the course of Alzheimer's, there was no room for discussions about the fate of Carol's father and his siblings, or about the cousins, spread across the world, who had learnt all those years ago that their cognitive future would be determined by a genetic coin toss.

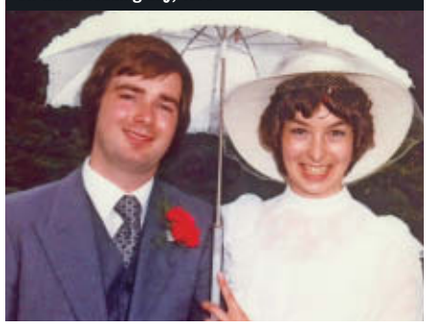
But when the history of that drug is written, it should begin with Carol Jennings and her letter.

A few months after that article's publication, I was sitting with Carol and her husband, Stuart, in their house in Coventry. Among the pictures on that mantelpiece of the couple and their children, there were snapshots from family holidays. A montage of one was labelled "Venice 2004". Beside a Father's Day card there was a photograph of Stuart and a grandchild that was captioned "Grandad".

It was the chronicle of a lifetime. A lifetime, Stuart insisted, that was well lived. "You know, if I knew what I know now, I would have still married her," he said. "We've had 44 years."

COURTESY OF STUART AND CAROL JENNINGS

On their wedding day, 1979



'She knew what was coming. She had seen Alzheimer's too often. You can know too much'

On holiday, circa 2010

Beside him, Carol, 68, started coughing. "Are you all right, darling? Oh dear, oh dear." He stopped talking and walked over to help. "She has minor seizures sometimes when she wakes up," he explained after she had settled down. "It's her brain. It's dying. It's imploding."

She was now looking at me placidly, oddly intent. "Carol's the one who helped us get here," Stuart said. "But she's at the end stage now. This is why it's so important that the story gets told."

We have, says Dr Richard Oakley from the Alzheimer's Society, "opened up a whole new era". We are "on the cusp" of real progress, he adds. In recent months he and his colleagues have been using a lot of phrases like this.

"This is the beginning of the end for Alzheimer's," one says. "For decades we have been telling anyone who will listen that there is light at the end of the tunnel. Today that light is just a bit brighter and a bit closer," another says.

The words "triumph", "milestone" and "remarkable" have been used.

The cause of this jubilation? In the past two years, two drugs have come out that are able to slow the progression of Alzheimer's symptoms by about a third. It is a measure of how low the lows have been that these fairly modest trial results represent such highs.

These drugs, lecanemab and donanemab, are not a cure. They are, in truth, a long way from one, but they are, scientists hope, a start. For the first time we have, to use the technical phrase, a disease-modifying treatment. We can interfere with the way the disease works, rather than merely mask its effects.

The drugs target a particular protein called amyloid. You find amyloid in the brains of healthy people, but you find it generally in higher concentration in the brains of people with Alzheimer's. And if you are one of the people unlucky enough to have familial Alzheimer's, you have a particular mutation that means amyloid accumulates in higher concentrations still – and means your symptoms start decades earlier.

What the drugs do is remove amyloid. And they work, sort of. They are not the cure that was promised 33 years ago in The Times. What they represent is something else that was promised that day: hope. For researchers, they are proof of principle. "This is the start," Oakley says. "It's not the end."

Stuart and Carol met through the church, he told me last June. They were both Methodists, although Stuart was a convert in adulthood. When he was 18 he had a motorbike accident and, while lying in hospital, was visited by the chaplain. He remembered it well. "It scared me to death to see a clergyman. I thought he had come to give me the last rites."

He hadn't. He had come to suggest that, since Stuart's motorbiking days were over at least for a few months, he should come to a youth club. Stuart did, and he kept coming. He found Methodism added a new dimension to his life, he said. That was not all it added.

A year later, a 22-year-old woman, another Methodist, started taking an interest in him. He now knows he was lucky. "She said if I'd been younger than 19 she wouldn't have gone out with me. It's good to know where you stand."

Carol, he remembered, "was such a bubbly bundle of fun. She was bright, articulate, enthusiastic." She was training to be a teacher. He put his hand on the older Carol beside him. "You wouldn't think so looking at her now, bless her, but she was a little bundle of dynamite." They married and began their life together. Stuart, increasingly drawn to the church, also began training for the ministry.

Then in the early Eighties came the first signs – the first intimations of the

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little protein that would come in so many ways to define their future. That was when Carol first noticed that her father was getting forgetful.

"He was making mistakes with his work. He was needing to be prompted," she recalled in a video filmed in 2010. They took him to the doctor. "He was diagnosed with Alzheimer's, which we'd never heard of."

Soon they would hear of little else. The same thing happened to her aunt, who was in her early fifties. "The next thing we knew, it was her brother too." Eventually, five of nine siblings had it.

Carol might not have heard of Alzheimer's until then, but she realised her relatives had been no stranger to it. She began piecing together her family history. Her grandfather had experienced the same problems.

Stuart played a video of a lucid and articulate Carol talking, while beside him she watched on. "I thought, there's something funny. This is the same family developing the same symptoms at a similar age. There must be something going on," she said from the screen.

At the time, Stuart said, there was an orthodox view that Alzheimer's had no genetic basis. Carol refused to accept, refused to believe that what she was seeing was simply a terrible fluke. She made a family tree. "I thought, this is interesting to someone." But she met resistance.

"Back then, you didn't argue with the experts," Stuart said. "It was completely the opposite of today. For her to keep pressing on was quite something." Eventually, in a team at St Mary's Hospital in London, she found some experts who would listen. In turn, in the family tree she gave them, with its uncles and aunts and dozens of cousins, those experts found a sample size big enough to test their hypothesis.

"Really big families are helpful," says Alison Goate, who was part of that team and is now director of the Ronald M Loeb Center for Alzheimer's Disease at Icahn School of Medicine at Mount Sinai, New York. "It was pretty clear, even from the nuclear family, there was something going on." You don't get that many siblings going down that early with dementia purely by chance.

The theory Goate and her colleagues were investigating was not that all Alzheimer's was genetic. They knew that could not be the case. In most people there was no statistical sign at all that it particularly ran in families. It was enough for the team's needs, though, that in just some examples there was a sign. If that was the case, they had a hunch that subset could tell us something about the whole.

"Clinically and pathologically, these cases looked extremely similar," Goate says. Families with genetic Alzheimer's seemed to get the disease earlier, but when they did it appeared to be the same disease. If so, that was not merely a clue. It was, potentially, a cheat code to unravelling the disease – to bypassing all the complexities.

Few diseases are simple. A body that is working well is a cascade of molecular processes and metabolic pathways, of atomic machinery and cellular mechanisms. A billion years of evolution has pieced together an inconceivably complex sequence of chemical reactions dedicated to the improbable feat of keeping a collection of cells moving, reproducing and thinking.

A body that is not working well is the same, but some of those processes have gone wrong. Finding out which, and how, is hard if it's, say, in the liver. If the malfunctioning processes are in the brain, an organ we still struggle to understand, the problem is near intractable. It was even harder in 1986, when Carol contacted St Mary's.

And yet there are some diseases that are a bit simpler: genetic ones, especially genetic ones that are clearly from one gene and that emerge in 50:50 chance through siblings and cousins. Here, scientists know that whatever is going wrong has been caused by a single mutation. All that complexity has been collapsed into a single cause. What a gene does is provide the code to make a protein. If you can find the gene that is mutated, you can find that faulty protein – and then you have a cause.

That was what Goate set about doing. She had samples of blood from Carol's family and a family tree of those who had Alzheimer's. What linked the two?

These days, with rapid sequencing technology, it would take longer to collect the blood samples than to find the gene. But in the Eighties? Well, Goate says, "Back then, we were in distant history." It was 15 years before scientists sequenced the first draft of the human genome. In the mid-Eighties, finding a faulty gene took a lot of work and involved a laboratory technique called southern blotting, along with some intuition that helped them cut corners.

People with Down's syndrome have a very high risk of developing Alzheimer's. They also have an extra copy of chromosome 21. To save time, the team focused on that chromosome.

'Back then, you didn't argue with the experts. For her to keep pressing on was quite something'

TOM JACKSON

Professor John Hardy

"What we did then we could do now in a few days or a week. It took us four or five years," Goate says. But they found it. There was a single mutation there in half the family members. In their case it related to something known as amyloid precursor protein. What it meant, practically, was that patients with this form of Alzheimer's had more amyloid. More amyloid meant, the scientists inferred, they had Alzheimer's. Simple. "For the first time, it gave us a target."

It was an invigorating time. Based on these findings, John Hardy, now chair of the molecular biology of neurological disease at University College London, published probably the most influential paper in the history of Alzheimer's. Its title was *The Amyloid Cascade Hypothesis*. All the complexity of the disease, all the damaged neurons, fractured memories and chemical imbalances? It started, he proposed, with amyloid.

Goate, and Hardy, believed they had uncovered the toxic headwaters at the top of the devastating neurological waterfall that was Alzheimer's: the amyloid cascade. "I thought, surely we would have a therapy in time to help Carol," Goate says. Carol was less optimistic. She always said that her hope was that whatever they learnt would benefit her children.

By the time Carol had filmed the video discussing her letter, she was employed by the Alzheimer's Society as an advocate for carers of people with young dementia. She did not know whether she had the gene, whether one day she would need a carer. She did not want to know. If she had it, each of her children had a 50 per cent chance of having it. There was a one in four chance that both did.

She was approaching the age where she would find out, though, without the need for a test. Stuart began to suspect they were already being shown the answer through little hints in her daily life.

"We all sensed at that stage that it was beginning to happen." Including her? "She never said. She used to get cross with me if I looked at her when something strange happened. She'd say, 'You think I've got it, don't you?' Which was very difficult. She always used to say, 'I could get run over by a bus tomorrow. Why worry about what's happening in three or four years?'"

In 2012, they were given the formal diagnosis. It is one thing to suspect; another to be sure. "She knew what was coming. She had seen Alzheimer's far too

'We all sensed that it was beginning to happen.' Including her? 'She never said'

many times. You can know too much. But then, within a week, she said, 'You know, we've got too much life to live. We've got to get on with it.'"

So they did. They went around Britain on holidays while she could. They visited their son in Edinburgh. And as she travelled bodily, mentally she slowly retreated. "The illness gradually stripped away who she was," Stuart said.

She awakened again at this point. He got up to wipe her mouth.

The problem – a problem – with early-onset diseases is that the world is not prepared for them. If you are a couple of decades older, the country expects you to get ill and be inactive. Mortgages, finances, employment – all are predicated on a particular length of working life.

But Carol only got her pension long after she stopped understanding what the word "pension" meant. It was very hard. "Alzheimer's is ongoing," Stuart said. "You lose the person gradually and end up caring for someone who is very different from the one you started with. It's a continuous grief.

"As a carer, you either dwell on what you've lost or you reflect and have gratitude for what you've had." If you do the former, he said, "It kills you."

When Carol dies, Stuart said, "I've got three hours to get her in a fridge." She wanted her brain to be donated to science.

She wanted it to be removed, cut open and prepared. Thin cross-sections to be carefully sliced and put on slides. Then, looking through a microscope, a pathologist would see the sticky plaques of amyloid, the toxic protein that had spent decades wrapping itself around her neurons. These are the proteins that today's drugs seek to remove.

The first clinician to look at these – or at least to understand what he was looking at – was Alois Alzheimer. In the early 20th century he examined the brain of a woman called Auguste Deter, who had been a resident of Irrenschloss, the Castle of the Insane, in Frankfurt.

In the preceding years, Alzheimer had been obsessed by her symptoms. He had watched as she became unable to name her husband or recognise common objects. She was alternately depressed and aggressive. When asked to write her name, she couldn't. In despair, she said, "I have lost myself."

In 1906, in her mid-fifties, she died. Alzheimer cut open her brain and saw the protein that today we call amyloid. He saw other things too. Alongside the amyloid plaques there were tangles of another protein, which we now call tau. If he had looked at older patients who had the disease at a later stage, perhaps there would have been more subtle abnormalities – the signs of inflammation, maybe, of years of neurological stress.

Carol's family helped simplify Alzheimer's. They gave the world a target. But had they simplified it too much? Was their target the right target? Was Carol's genome not, in fact, a vital clue? Could it instead have been a trap?

This was what, starting in the 2010s, began to worry John Jennings, Carol and Stuart's son. "I had a bit of a crisis of confidence," he says. For 20 years, scientists working on the amyloid hypothesis had developed drugs to attack amyloid. Those drugs had succeeded in the laboratory in animal trials and then passed human safety trials. But then, a decade and £1 billion later, one after another they failed.

John was just one when his mother sent her letter. He had grown up with Alzheimer's and amyloid. "Whether we like it or not, our family is totally nailed to the amyloid hypothesis." Now that hypothesis, which had dominated the field, looked increasingly shaky.

John cannot remember the failure that caused him to question it ("There have been so many"). He can remember feeling responsible. "I thought, has our existence derailed everything?"

Scientists began to form camps. Researchers began to identify as "amyloid" or "anti-amyloid". Egos, funding and careers became involved. Anger, accusations and incivility followed not far behind.

"People took great delight in trials failing because of the camp they'd decided they were part of," John says. "It became exhausting. They took delight in the downfall of their colleagues. It was ridiculous squabbling."

Then three years ago, almost after everyone had given up, a drug called aducanumab made it through trials. In the data, if you held it up to the light just right, there was a hint it had done something. The arguments, if anything, became more furious.

A year later, another drug, lecanemab, did better – well enough that there was no doubt, no room for argument. Then last year a third, donanemab, matched its performance. The amyloid hypothesis was true after all. The money had not been wasted.

And yet, was it really the whole story? Will better amyloid drugs come along? Will we stop the cascade before the waterfall of proteins drowns the brain? Or is it possible that we should be ➨

looking at other targets too? For John, of course, the question is not academic.

He has been tested for the gene. He had to be. He is part of a trial to see if drugs could work even better if taken early. But just as he does not know whether he is on the drug or a placebo, neither does he know if he is one of those in whom the amyloid is already accumulating. He does not know if he has the mutation. Somewhere, there is a computer that knows John's future. In its hard drive, perhaps in a spreadsheet, there is the genetic reading that will define the second half of his life. He has not asked to see it. Does he not want to know?

"I go back and forth. My thinking is all over the place. It's not linear." He has been following the developments closely for the past three decades. His sister, Emily, has not. ("She just tells me, 'Let me know when they actually have something.'")

His is a position of cynical optimism. Or maybe positive nihilism. "I've got myself into a state where I can read the research and be interested in it, but still assume that everything's going to fail. And then when it doesn't, it's a nice surprise."

That is how he views the latest drugs. They are obviously nice. For many the success was a surprise. They are also, clearly, not enough.

Goate now regrets that early optimism, regrets that too many were taken in. "We really ought to have been developing therapies against different components of the disease," she says. "If you look at cancer or heart disease or any other common disease, we don't just develop drugs against one target. We develop drugs against multiple targets and then we decide based on the individual which drugs are most likely to be effective."

Today, though, at last we are. Oakley says, "There are many others. There are nearly 150 disease-modifying treatments now in clinical trials... And actually, for them, amyloid isn't the primary target or the secondary." They are combating tau, inflammation – lots of different points in the cascade. "I don't even think amyloid is the third target. So there are many other targets that people are looking at. We have had," he admits, "a bit of a journey."

There is now something of a detente among the "camps". There is a growing acceptance of where that journey is taking us – several drugs, taken together, not as a cure but as a means of control. Many think by analogy of another disease that affected different people in different ways: HIV. Once we had the first antiviral, AZT, others followed.

Alzheimer's, John thinks, has had its "AZT moment". He also knows that, for him, it may not be enough. "The way that I have been thinking about it recently is that, at the lower end of the range, I've got ten years, which is simultaneously quite a long time and not long at all. So I just need to cram as much into that time as possible."

Carol and Stuart's son, John Jennings

'At the lower end of the range I've got ten years, which is quite a long time, but not long at all'

The Alzheimer's Society helped put me in touch with Stuart last year. Before the interview, it sent a document advising me how to interact with and write about people with dementia. Don't use words such as "sufferer", "burden" and "victim", it said. During the interview acknowledge the person with the condition as well as the carer. Try not to disempower them. Don't make assumptions.

It was hard. Sometimes Carol looked at me and it felt like she was watching and understanding. A lot of the time, I forgot she was there. When I did remember, it was because Stuart was tending to her.

Has it been helpful, I asked, that they have their faith? Almost immediately, I apologised. "Sorry, that's a trite question." "Yes," Stuart said. "It is."

He went on, "Caring for someone with dementia is a human problem. It is more about wrestling with humanity than faith... It's about what it is to be human, what it is to be a person. And the extent our memories are who we are."

In a simpler world with a simpler disease, Carol's would have been a simpler tale. Through her dogged persistence, in the face of institutional intransigence, we would have had a target. That target would have provided a "magic pill", as Hardy once wryly referred to his research assumptions in the Nineties. "One ring to rule them all," he added, in a *Lord of the Rings* reference. But Alzheimer's is not simple. Not at all. And, unlike a fantasy novel, there is no deus ex machina.

In the time that Carol had left, Stuart said he had different goals, both bigger and smaller. He wanted Carol's work to be remembered. He hoped it had made, and will yet make, a difference. He also wanted to know that when the disease that became her life eventually took her life, it would be after a good life.

"I like to think when she stands before her maker, it will be with a sense that she was loved and cared for," he said as I left.

Carol died in Stuart's arms at 9.30am on Good Friday this year.

Speaking a bit over a fortnight later, he says he is adjusting to a different life. It is a life without routine, without support staff in the house and where he can go out when he wants. "It's strange," he says. "A presence has gone. She wasn't the Carol that was, but she was a presence. The house is really empty."

In her final year, she lived to see – if not understand – yet more advances. In treatment, the drugs targeting amyloid continued to show promise, albeit not spectacularly so. UK regulators, weighing up costs and side effects, have yet to approve them for use. In diagnosis, blood tests that looked for amyloid, as well as other proteins, looked set to revolutionise primary care.

If the past 40 years showed her and Stuart anything, it is that this is not a simple disease and those researching it need all the help they can get. Which is why Stuart is so proud that she achieved her final wish. It was difficult on a bank holiday, and they weren't sure they would achieve it, but they managed to get her to a refrigerator within three hours. By now, scientists will have extracted her brain, preserved it and begun studying it.

Separated onto thin slides, the slices will be examined – the strata of Carol's self. Labelled, catalogued and refrigerated, they are the neurons that recorded the memories of a life: love, faith, holidays, children. They are the neurons that, almost four decades ago, spotted something odd in Carol's extended family. They are the neurons that, for whatever reasons, fired in such a stubborn arrangement that their owner persisted in questioning this oddity even when scientists assured her it was mere chance.

They are also the neurons that, decades afterwards, in an irony that Carol always expected, became slowly and inexorably strangled by the very protein she helped identify. Now they are the neurons, pickled and preserved, that will again help scientists in their decades-long challenge of understanding Alzheimer's. In death, she still has a part to play in the battle that defined her life. "That was my last promise to her," Stuart says. ■

A documentary, The Jennings vs Alzheimer's*, will air on BBC2 at 9pm on May 13. alzheimers.org.uk*