Memories of the Future

Can a simple pill make us remember? And if it can, should it?

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So a man goes to the doctor, and the doctor tells him there is bad news. In fact, there is bad news and really bad news. Which does he want first?
'The really bad news.'
'The really bad news is that you have Aids.'
'Oh my God. And what's the bad news?'
'The bad news is you also have Alzheimer's.'
'Could be worse,' the man says. 'At least I don't have Aids.'

This year may be remembered as the year in which we all got the really bad news. Alzheimer's competes fiercely with HIV to be the disease of our times, and it is difficult to get through a day without hearing someone say, 'Now where did I put that thing - I must be getting Alzheimer's.' The disease has entered our culture far beyond the level of dubious internet jokes: bookshops are increasingly busy with fiction and memoirs in which someone can't recognise their own children; celebrity interviews feature poignant moments in which actors (in this case David Hyde Pierce from Frasier) will recall, 'The last time I got an Emmy, I brought it to my dad. He was so excited because he couldn't wait to tell my mom - and she had died four years before.'
There are more symptoms of Alzheimer's than just severe memory loss, but it is memory loss that provides the most disturbing details of the disease, and the symptom that, as healthy individuals, we fear most. We may approximate what it is like to lose our sight by closing our eyes and bumping into things, and to go deaf by blocking our ears; in both cases our memories will help us manage. But one cannot imagine what it is like to have no memory. We may forget our keys, but we don't usually forget where our front door is; we may forget where we left our car, but we do not forget that it is somewhere in the car park.
Psychologists have long since tired of telling each other that we are our memories, but it is as potent a thought as ever. It is no wonder that severe memory loss can be a disaster for those who experience it and those who observe it.
Alzheimer's also affects the way we think about memory. Although it is only one of several diseases of dementia, its prominence and prevalence in an ageing population has turned the study of how we remember into a booming business. Memory clinics - at which standard tests are conducted and advice offered - were rare 20 years ago, but are now a common feature of NHS Trusts. Never have so many psychologists gauged our ability to recall a simple list of words. Never has

the internet been able to supply such a wide range of teas and herbs and quick fixes to get us through exams - just at the time when our anxiety about the effect of computers and mobiles on our ability to retain and process basic information has never been greater.

Until recently, memory loss was not considered a trait one could do much about. This is no longer the case. Our understanding of the way the brain functions with regard to memory has advanced rapidly since we first learnt about synapses at school, and we are now able to pinpoint its decline and hint at its repair. Nowhere is our quest for total recall more ambitiously pursued than in the laboratories of drugs companies, making something that not long ago would have existed only in the movies: memory pills. If the work is successful there, it may change the landscape for us all.

In a low white building in Irvine, California, about 90 minutes' drive from Los Angeles, Cortex Pharmaceuticals is a modest start-up company with 21 full-time staff and 48 patents. The patents describe compounds designed to treat several neurological and psychiatric disorders, including Alzheimer's, autism and schizophrenia. In a recent presentation to prospective investors, the company estimated that the worldwide market for drugs for these diseases is worth $51.9bn.

A few weeks ago, in a darkened boardroom decorated with a large American flag, Cortex's Roger G Stoll took me through a slide show of his company's achievements and goals. There were the usual Powerpoint bullets and graphs, and then some illustrations of monkeys performing tasks in front of a screen. The monkeys were called Bucky, Newton and Wilbur, names they shared with other scientific pioneers, and they were given compounds labelled CX516 and CX717. Their reactions to these had the potential to improve the future happiness of the next generation of humans.

The drugs they were given are known collectively as ampakines, named after their impact on the AMPA receptors in the brain. It acts on the predominant chemical neurotransmitter that plays a vital gate-keeping role in the exchange of information between cells and underpins the formation of many types of memory within the hippocampus, the site where short-term memories are converted into long-term memories for storage in other brain areas. Ampakines are also thought to increase the strength of signals between brain cells at the very points of connection adversely affected by Alzheimer's.

Not that Bucky or Wilbur cared much about this. Their main incentive was sugar. In experiments conducted for Cortex last year, one of the monkeys was strapped to a chair and saw an image flash on a screen. The image - a piece of fruit, perhaps, or a table - was then removed, and after a period of between 1 and 60 seconds it appeared again, this time accompanied by several other images. The monkey's job was to identify the original picture by moving a computer cursor. 'If he does it correctly he gets a little squirt of juice and is a happy player and wants to go on,' Stoll says.

A short video showed the great speed at which the animals worked - it took about one-and-a-half seconds for the monkeys to move the cursor. The tests lasted for about 90 minutes, and six monkeys were used over several days. Their reaction time was monitored alongside their success rate and the results were measured

against the varying strengths of the drugs administered before the test. These figures were then compared with the results of placebo trials.
Six chimpanzees were used in all, and the success rate without the drugs was high: between 70 and 80 per cent of the objects were correctly identified. Even at low dosages, the intake of ampakines boosted performance markedly, and as the number of milligrams increased, so did the monkeys' hit rate. In another test, the monkeys took the drugs after sleep deprivation, an experiment that caused much excitement among officials in the US military, who were keen to boost the alertness of their pilots and special operatives without the jitters that come from caffeine. Again, the chimps came through. Those who were refused sleep performed less well than those who had slumbered; but their results levelled off when the tired monkeys had their neurotransmitters spiked with CX516.
But recently there was a setback. An international trial of 175 people with Mild Cognitive Impairment (MCI), a condition in which patients display serious but manageable levels of memory loss, and which is often a precursor of Alzheimer's, showed disappointing results: those taking CX516 performed no better in a 15-word test than those on the placebo. Cortex and Servier put forward several reasons for this failure, claiming that the dosage of the compound was too weak and that it had a very short potency of under an hour. 'We should have killed CX516 five years ago,' Stoll tells me, in the same breath as he says that the latest compound, CX717, is designed to remain effective for 10 times longer, and is 50 times more powerful. 'The early results,' he says, 'make us very optimistic.' There is no clue yet whether these treatments will one day boost the memory of the healthy. But what a market that would be. The board of directors at Cortex includes Carl W Cotman, a professor at the University of California, Irvine, where he also runs the Institute for Brain Aging and Dementia. Cotman is a great believer in the potential of ampakines, but he recently made headlines by showing that memory and cognitive function are quite capable of being boosted by substances you can already buy at the shops.
In February, he told the American Association for the Advancement of Science of his diet experiments with beagles. Dogs who had their normal meals laced with vitamins C and E and a nice selection of fruits and vegetables were compared to dogs who ate normal fare. Younger dogs on the special antioxidant diet showed no great improvement when challenged to distinguish the odd object in a group of similar ones, but the benefit to the older ones was unmistakable. But should we be surprised that the factors that are well established in limiting the risks of heart disease can also have a beneficial effect on our memories?
Tanned and silver-haired at 63, Carl Cotman works in an office strewn with copies of his own publications and certificates of his achievements. He's an amiable man and I suspect he's a favourite among his students. But there is no mistaking the frustration when he talks about the wider reaction to his work. His beagles have already displayed a natural way of protecting brain cells from massive oxidative damage (what he calls 'molecular rust') and he suggests there is already much human literature consistent with his animal studies, albeit largely retrospective and anecdotal. He believes that the correct diet may delay the conversion of normal ageing to dementia by 20 or 30 per cent. 'The problem is, how do you prove it?' he tells me. 'How the heck do you do a placebo-controlled

diet study in which people get the same food for breakfast, lunch and dinner for two years? It ain't gonna happen.'

He cites a recent study from the Mormon community in Cache County, Utah, which showed that a combination of vitamin A and C delayed the onset of Alzheimer's. 'Significantly - it almost halves it. You should say, "Holy smoke!" But a lot of people don't believe it, because it's a survey and not placebo-controlled.'

Cotman and colleagues have proposed an exhaustive clinical trial involving 4,000 patients and lasting five years, but he fears the cost of about $35m will be prohibitive. He also doubts whether funds will be made available to finance an irrefutable large-scale study to show that elderly people who are physically fit have less brain atrophy than those who take no exercise. He has conducted some treadmill tests on rodents and found they increased the molecule BDNF, a natural memory booster. Human trials in those over 65 have shown that over a six-month period those who underwent aerobic walking for 45 minutes a day three times a week performed better on attentive and decision-making tests. Another experiment has suggested that exercise increases neurogenesis (new neuron formation). 'So good Lord,' Cotman says. 'I mean, what does it take to change people's habits? I remind myself sometimes when I don't feel like working out, "Hey Carl! Believe your own stuff!"'

Dr Cotman began studying ageing about 25 years ago, at a time when most of his colleagues were more interested in child development. He had seen the graphs predicting a large increase in the elderly caused by a population boom and science's ability to keep people alive for longer, and he had studied the figures suggesting that 40 per cent of those over 85 will develop dementia. Worldwide, there may be between 18-25m people with dementia (the UK figure is about 750,000, with 18,000 under the age of 65). Alzheimer's accounts for just over half of these cases, and the figures for Mild Cognitive Impairment may be roughly the same. By the middle of the century, those over 85 will be the fastest-growing sector of the Western population.

The basic knowledge of Alzheimer's was well established when Dr Cotman began his work in the Seventies, but had advanced relatively slowly since Alois Alzheimer had first met his 51-year-old patient Auguste D in Frankfurt in 1901. She was disorientated and confused about her name, and in the following years she became increasingly delirious. By the time she died in 1906, Dr Alzheimer had ruled out diagnoses of what we now know as Parkinson's, Huntington's or schizophrenia, and when he examined the stained slides of her brain under a microscope he found something he had never before noticed in the cortex: a mass of brown spherical 'plaques' obstructing communication between neurons and a darker knotty string of 'tangles' that choked neurons within their cells. The formation of these plaques and tangles is part of the normal process of brain ageing and only becomes a problem when the proteins that form them - known as beta-amyloid and tau - are produced in excessive amounts.

Cotman is fond of quoting Pythagoras as an indication of how long we've known about the symptoms of mental decay - a natural cycle that returns us to the imbecility of childhood. But it is only with advances in molecular biology and genetic cloning that we have been able to grasp how this process works.

While ampakines and other drugs target specific areas in the hippocampus,

memory relies on several areas in the brain to function effectively. The frontal lobes draw on memory to make decisions and manage information, while the temporal lobe stores and processes past events, and MRI scans show the damage to these areas in Alzheimer's patients. Recently, Nature published findings from two American studies that independently located for the first time the 'penny-sized' area in the cortex responsible for the retention of all short-term memory; it was suggested that damage to this spot alone might have a huge impact on our cognitive abilities.

Drugs such as Aricept, Exelon and Reminyl work in a similar way to restrict an enzyme that blocks acetylcholine, essential for communication between neurons. The newer drug Ebixa, which helps block the release of excessive glutamate that damages brain cells, appears to slow down the advance of Alzheimer's even in later stages. One day, there may be a vaccine. In the meantime, the best treatment will be combination therapy - a cocktail of drugs. But a few weeks ago a dampener was cast over the efficacy of all the existing drugs at a conference at Johns Hopkins University, Baltimore, when a group of specialists at the Alzheimer's unit doubted whether they would cause any reduction in the huge increase of cases for decades. 'You can name 11 fruits in a minute instead of 10,' said one professor. 'Is that worth $120 a month?' Reminyl was originally made from the bulbs of snowdrops and narcissi, one of many natural compounds believed to be beneficial to memory and cognition. The best known is extracted from the leaves of the ginkgo biloba tree, although the results of a large-scale American study released in 2002 suggested it had no effect on the memory of healthy older people. Earlier this year, a small-scale study conducted in Edinburgh showed verbal memory improved significantly among men aged 55-75 given carbenoxolone, a compound based on liquorice root thought to block the production of the stress hormone cortisol.

Other indications suggest cholesterol-lowering statin drugs may help, as may oestrogen intake in post-menopausal women before Alzheimer's starts. Huperzine, an alkaloid from a natural herb, has been used for centuries in China as an anti-ageing treatment and memory booster, and when tested in cell cultures was found to save cells from beta-amyloid degeneration. There are also internet-ready products such as Intelectol ('Boost your brain power with periwinkle extract!') and Brainquicken (a 'neural acceleration product'). The latter comes with a 110 per cent guarantee, which enables unsatisfied customers to get their money back and a 10 per cent 'gift', even if they've swallowed the entire bottle. Then there are apothecary-style products: cat's paws and the saliva of the Gila monster lizard.

From the earliest school exams onwards, memory has traditionally been about learning lists. There are spatial and olfactory techniques as well, but list-learning is still the fundamental way memory is tested and the clearest indicator that enhancement has worked. Doctors apply a traditional list of questions, known as the Folstein Mini-Mental State Exam, to determine whether a patient may need a brain scan for Alzheimer's, and psychologists employ traditional word lists - train, garden, table - to test their latest experiments. Traditional and novel methods of memory enhancement can be found in a tall stack of books that rises by about a foot each year, and their authors usually have the air of PT Barnum

about them. Most rely on a combination of visualisation systems and mnemonics. In The Memory Book, for example, which claims more than 2m copies in print, Harry Lorayne and Jerry Lucas use a familiar linking process to tie the new and unfamiliar with something already understood. The best known of these is probably the treble clef scale EGBDF, recalled as Every Good Boy Deserves Favour, but then things get a little more complex, relying on visual pictures: to remember the fact that someone comes from Maryland, Massachusetts, 'You could picture a girl named Mary landing among a mass of old people who chew and sit.'

At the department of psychology at the University of Leeds, Chris Moulin teaches learning techniques to undergraduates, and tells his first-year students that they are more likely to remember a word if they engage with it. 'You rate a list of words for pleasantness, and then another list you rate as to how many vowels they have, and the first one you'll find much easier to remember.'

Moulin and his colleagues are engaged in studies to repair learning in Alzheimer's patients without chemical intervention. They also use standard word lists, and some olfactory tests, as the main indication of the success of their inquiries. When I ask what these words actually were, he is reluctant to divulge them. He fears that people might rote-learn them to show they do not have memory problems, the same way he has seen people gen-up on the standard Alzheimer's quiz. 'In the waiting rooms of memory clinics, there are always people going "Wednesday, Wednesday... Tony Blair, Tony Blair."'

I met Moulin at the university, in a room whose walls are covered in charts describing past memory experiments. He admitted somewhat sheepishly that he collected shopping lists in an album, and told me that his fascination began after he found a list on the floor of a memory clinic that read 'bin liners, memory clinic, lunch'. His favourite is a piece of paper from a supermarket with just one word on it: oil.

Moulin has conducted tests with Alzheimer's patients in which he has given them more time to learn things, and others in which he has consistently repeated words, but to little effect. Unlike people who have suffered from amnesia, those with Alzheimer's usually have little residual memory to work with. 'But this is now a happy story,' he says, confirming the effectiveness of a notion known as 'errorless learning'. This work runs against the usual practice of learning by trial and error, and limits the mistakes one can make. 'It's so simple,' Moulin says. 'Initially I might say, "I'm thinking of a word beginning with the letters wa" and you might get warmth, wagon or water. So I would say, "No, it's wafer." In the other scenario I would say, "I'm thinking of a word beginning with wa and it's water." So basic, but it can increase learning by 20 or 30 per cent.'

This can't help recover memories that have already been lost, but it is an effective way of retraining those with a particular difficulty in remembering names and faces. But Moulin says he encounters some difficulty even with this fundamental research, for most groups of Alzheimer's patients are gathered together with funds from drugs companies, and it is increasingly difficult to find 'clean' patients who are not taking something.

Some of the research at Leeds is conducted on the internet. One project examines the 'use it or lose it' hypothesis, by checking memory loss in relation to crossword

compilation. All participants - ranging from those who never tackle crosswords to those who do them every day - are asked how frequently they forget why they went into a specific area in their house, and how often they put something in an inappropriate place (ie butter in the bread bin).
The focus is always on what goes wrong, but Moulin suggests there may be some advantage in having a failing memory, or at least there could be, if it didn't usually indicate some deeper malaise. He also notes that as we get older, our memory gets more positive. 'A large proportion of people in their thirties will say they had a lousy childhood, but by the time the same group are in their eighties only about 5 per cent are still saying that.'
Hollywood's latest film about memory, with the difficult-to-remember title Eternal Sunshine of the Spotless Mind, embraces the notion that problem memories - a relationship gone sour, bearing witness to a traumatic accident - may be erased by a painless electrical editing of neurons. In a neat parody of the Folstein test, the film's website contains a list of questions that aim to determine whether you may be suitable for this treatment, including, 'Do you think your life would be better if certain people were never born?' and 'Do you trust radical medicine?' A few days after the film opened in the US, The New York Times carried a report about a blue pill called propranolol currently undergoing a small-scale test at Harvard Medical School.
Propranolol is a beta-blocker that affects stress hormones in the brain, and may, if taken shortly after witnessing a particularly dramatic scene, be able to prevent the memory of it taking hold. This may apply equally to both positive and negative events, though only those of a highly charged emotional nature. In other words, the more we understand about the way memory imprints itself on our minds, the less we may be able to know. Some will inevitably regard memory suppression and enhancement as dangerous science, though probably not those with post-traumatic stress disorder, or the carers of people with Alzheimer's.
There is no question researchers like less than 'How long until the cure?' There is no cure in sight; when pushed, the people at Cortex will express hopes of accessible and effective new treatments within five to 10 years, much too long for many. They are more certain that the challenge of defining how and what we should remember in our lives is far greater than the solutions offered by even the smartest medical fixes or tests with lists. Chris Moulin's family joke with him that as soon as medicine discovers a way of restoring and protecting our memories, he will be out of a job. In fact, his job will only just be beginning.

www.alzheimers.org.uk