Science & technology

Down's syndrome and Alzheimer's disease

Fortune's wheel

Volunteers with Down's syndrome could help the search for Alzheimer's drugs

DEMENTIA LOOKS likely to dominate old age in the 21st century. A study in this week's *Nature Medicine* reckons the number of Americans developing it each year will rise from 500,000 in 2020 to 1m in 2060. And though drugs that have some effect on Alzheimer's disease, dementia's most common manifestation, have recently been assessed in America and Britain, not everyone is convinced.

The European Union's drugs regulator, for example, refused last summer to approve the first of them to come across its desk, though it has partially reversed that decision. And in England, despite regulatory approval, the National Health Service does not yet offer them. Many researchers suspect they might work better if given earlier, perhaps even preventively. The easiest way to find out, they say, is to conduct clinical trials on people for whom the onset of Alzheimer's is nearly guaranteed: those with Down's syndrome.

As the life expectancy of people with Down's has risen, it has become clear that most will eventually develop Alzheimer's. Studies suggest 70-88% will do so by the age of 65. In the general population the comparable figure is 8-10%. Until now, though, trials of Alzheimer's drugs have excluded those with Down's, meaning doctors feel they cannot safely prescribe them to those individuals. Including people with Down's in future trials could not only offer them treatment, it might also herald a future of Alzheimer's prevention for all.

The link between the conditions is a genetic hiccup. Those with Down's have an extra copy of chromosome 21 in their cells. This brings with it an extra copy of the gene encoding amyloid precursor protein (APP), a molecule involved in the growth and development of neurons. Unfortunately, APP is also—as its name suggests—the precursor in certain circumstances of a smaller protein, beta-amyloid, that forms clumps called plaques in the brains of those with Alzheimer's. The extra gene copy means people with Down's have higher levels of APP and, therefore, more beta-amyloid. As a consequence, virtually all those with Down's have beta-amyloid brain plaques by the time they are 40. About 15 years later, most have dementia.

A cascade of problems

Though Alzheimer's in those without Down's rarely has a clear genetic cause, the connection (which emerged in the 1980s) between APP, beta-amyloid and dementia suggests an underlying mechanism. In 1991 John Hardy, a neuroscientist now at University College, London, and his late colleague David Allsop (then at Queen's University, Belfast) thus proposed the amyloid cascade hypothesis. This posited a build-up of beta-amyloid in the brain to be the driving force behind Alzheimer's in all those affected by it, whether they have Down's or not. Other signs of Alzheimer's, such as brain shrinkage and tangles of a second abnormal protein called tau, are thought to come later.

The amyloid cascade hypothesis re-

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mains the most influential explanation for how Alzheimer's develops. A search is thus now on for drugs that get rid of beta-amyloid. Trial after trial has failed. But two substances have been found to do the job. These are artificial antibodies called lecanemab and donanemab that bind specifically to beta-amyloid, flagging it for disposal. However, though both drugs slow cognitive decline, they do not do so by much. After 18 months, dementia scores for people receiving lecanemab had deteriorated 27% less than those receiving a placebo. For donanemab, it was 35%. Ideally the drugs would stop decline completely—or even reverse it. Given that 20% of people receiving lecanemab and 24% of those receiving donanemab develop small (though mostly harmless) brain swellings and brain bleeds, scepticism that the new drugs are worth it is understandable.

Critics of the amyloid cascade hypothesis reckon the antibodies' lacklustre performance is because beta-amyloid is the wrong target. They think tau, or even APP itself, could be more important. Others, who still support the Hardy-Allsop explanation, suspect the two drugs might work better if given earlier in life. They suggest that by the time most patients take them, the illness is too far gone to be stopped by amyloid removal alone. If that is true, anti-amyloid drugs might be better suited to prevention than treatment.

An obvious way to test this would be to run clinical trials on a cohort for whom eventual Alzheimer's is a near certainty, but before symptoms set in—in other words, those with Down's syndrome. Obvious, but radical. Companies are wary of including those with confounding conditions in their trials, for fear of affecting their results. And obtaining truly informed consent requires extra effort, to make risks understandable to them and their families.

That is starting to change. ALADDIN, a trial of donanemab for those with Down's, organised by researchers at the University of Southern California, will start later this year. And an existing trial, ABATE, which is testing a different anti-amyloid immunotherapy in America, Britain and Spain, already includes them. This turnaround owes much to lobbying by people with Down's and their families.

One notable moment was a speech to an American Congressional hearing in 2017 by Frank Stephens, a board member of the Global Down Syndrome Foundation who, himself, has Down's. In the three years following this speech, which received a standing ovation from the assembled Congressfolk, annual funds disbursed by the National Institutes of Health for research on Down's rose from $35m to $111m. By 2023 the figure had risen to $133m. Mr Stephens says it changed scientists' attitudes towards studying the syndrome.

These trials will require care to ensure any risks associated with high beta-amyloid in the brains of people with Down's are taken into account. Last year a post-mortem study of brain tissue from 15 people with the condition found lecanemab bound to amyloid stuck in the walls of blood vessels in all analysed tissue. That binding is thought responsible for the brain swelling and bleeding seen in the general-population trials. People with Down's may thus be at higher risk of those side-effects and might need lower dosages.

Yet if the drugs prove safe and effective when administered before the onset of symptoms—or even before amyloid build-up—it could offer people with Down's the hope of several extra years, maybe even a whole life, without Alzheimer's. For others, in whom the onset of Alzheimer's is harder to predict, researchers would still need to improve early diagnosis to reap the benefits fully. Work published in 2024, in *Nature Aging*, in which blood proteins were used to help predict Alzheimer's ten years before conventional diagnoses could be made, suggests that may soon be possible. Moreover, the drugs' performance will reveal whether the prevailing understanding of Alzheimer's is correct. Thirty years on from the amyloid cascade hypothesis, such a test is well overdue. ■

Huntington's disease

Dancing with death

CAMBRIDGE, MASSACHUSETTS

A new explanation of a fatal genetic condition opens novel avenues for treatment

HUNTINGTON'S DISEASE is horrible. It is also odd. Illnesses caused by inherited aberrant genes are mostly what geneticists call "recessive", meaning someone must receive defective versions of the gene involved from both mother and father. Huntington's, the symptoms of which start with involuntary jerking, mood swings and memory problems, and end with death, is "dominant"—meaning only one parent need be a carrier to pass it on.

Since a dominant gene's ill effects cannot be covered up by a functional version from an unaffected parent, the faulty DNA is generally purged by natural selection. This explains why dominant diseases are unusual. But Huntington's second, self-preserving, oddity is that unlike most genetic disorders it rarely manifests until well into adulthood, giving plenty of time for it to be passed on. The result is families where half the members are living under premature death sentences.

So far, attempts to develop drugs to commute those sentences have failed. But that may change. Steve McCarroll of Harvard University reckons one reason for this failure is that the accepted explanation of how Huntington's plays out at a molecular level is incorrect. That may have led drug companies up a blind alley. As they outline in *Cell* this week, he and his colleagues have a better explanation—one that could potentially alter the direction of pharmaceutical research.

Only with DNA sequencing did what is happening in Huntington's start to be understood. People affected are victims of a particularly long chromosomal "stutter", in which three letters of the genetic code (CAG) are repeated over and over again (CAGCAGCAGCAG). The repeated DNA is in the gene which encodes a protein dubbed huntingtin, which is produced in brain cells.

For those born with fewer than 36 of these repeats, the stutter does not matter. They are disease-free. Those with 36-39, however, may develop symptoms. And those with 40 or more definitely will. Moreover, the more numerous the repeats, the earlier the symptoms present themselves and the younger the person dies.

Given these facts, the generally accepted explanation has been that huntingtin proteins with too many of the extra amino-acid units encoded by the stuttering sec-