A cure for dementia? – what happened?

- Jonathan Stone, Professor Emeritus in Neuroscience
- University of Sydney

I got into neuroscience when I was young

Over the decades I did other things.

Married young …….

With 7 grandkids

But still a neuroscientist

A cure for dementia? – what happened?

- This article appeared early this April (2026) in newspapers in several contents.
- Behind it is a recent article from a UK group – well packaged for publicity.
- The group had looked at the progress of patients diagnosed with dementia, and offered one of several new drugs – they were antibodies – designed to extract from their brains a peptide (a short protein) know as Aβ, or beta-amyloid.
- In the hope that lowering the amount of Aβ in their brains would reverse/stop/slow the slow but relentless progress of cognitive loss that is observed in dementia patients.
- The drugs were successful in removing Aβ from the brain – but not in ameliorating their cognitive loss.
- And there were damaging side effects.
- Would this still-expensive drug benefit patients? The authors were not encouraging.
- Had the whole venture of creating them been in vain?

Breakthrough £90,000 Alzheimer's drugs unlikely to benefit patients, report suggests

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James Gallagher
Health and science correspondent

Influential analysis has concluded that "breakthrough" Alzheimer's drugs are unlikely to benefit patients.

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Amyloid-beta-targeting monoclonal antibodies for people with mild cognitive impairment or mild dementia due to Alzheimer's disease

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Collapse all Expand all

Abstract

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Rationale

Alzheimer's disease is a neurodegenerative disorder and the most common cause of dementia. Aggregated amyloid-beta protein deposits are implicated in its pathogenesis. Amyloid-beta-targeting monoclonal antibodies (sometimes represented as Aß-mAbs) are potentially disease-

So, what happened? And does it matter?

The rest of this talk is about what happened; you can make up your mind whether it matters or not.

People have long been intrigued and concerned by the loss of cognition in older people.

- Descriptions of cognitive loss can be found in writings of Greek philosophers (Pythagorus), Roman writers (Lucretius), similarly ancient Chinese writers (Hua To). Historians of dementia have traced these writings in a scholarly way.
- Pythagorus (800 BC) considered human life to go through 5 stages, the last beginning at the age of 81 (yikes), marked by a breakdown of cognition – senility.
- Shakespeare, writing 2,400 years later (17th Century) wrote a soliloquy in his *As You Like It* , in which he described the 'life of a man' in seven stages, the last of which was 'childishness and mere oblivion'.
- Obviously, if one dies young, you will avoid what is a personal tragedy for the individual and our carers.
- Despite these views, most present-day websites designed to offer advice for sufferers and carers argue that 'dementia is not a normal part of ageing'. It is a disease – and that implies the hope of a cure.
- And it was in pursuit of that cure that big pharmas developed the drugs tested in the article we began with.
- So one of the issues to which those data are relevant is whether dementia is a disease? Or a fate?

So, why did that study focus of the peptide Aβ?

- Early ideas of the causes of dementia were expressed in the ideas of their time:
  - Ancient writers explained it a breakdown of the balance of ‘biles’ in the body
    - By the 17th Century, physicians were beginning to attribute the failure of the aging brain to the aging of the vasculature – not a bad guess, since the brain is one of the most vascular organs in the body.
    - But what was the connection?
    - My own view is that dementia is due to vascular pathology - but late in the 20th Century, the understanding of dementia took a different turn, made possible by some extraordinary new techniques.
    - And some pioneering and brilliant science – with a fatal flaw of reasoning.

So, what was the fatal flaw? That meant that the hypothesis that the toxicity of Aβ is the fundamental drive of cognitive loss in the aged would fail?

Its flaw was identified in this paper:

*Smith MA, Joseph JA, Perry G (2000) Arson. Tracking the culprit in Alzheimer's disease. Ann N Y Acad Sci **924**, 35-38.*

Basically, the authors argued, with more insight than evidence, that Aβ is produced by the ageing brain to protect its neurones from the stresses that were damaging it.

That Aβ was ubiquitous in the ageing brain because it is a first-responder molecule, trying to save the brain.

Why do we find firemen so consistently at fires – because they are trying to quell the fire. They are not the arsonist.

Arson

Tracking the Culprit in Alzheimer's Disease

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ABSTRACT: By focusing on the lesions in Alzheimer's disease, and regarding them as either critical or irrelevant, researchers may have missed much regarding the origin and pathogenesis of this disease. In this article we consider that the lesions are so obvious not only because they are pathognomonic for Alzheimer's disease, but also because they represent a major departure from normal physiology. We suggest that these myriad pathological changes are homeostatic compensatory mechanisms to aging.

KEYWORDS: Alzheimer's disease; Amyloid; Antioxidant; Homeostasis

But first, the brilliant new science:

- The new technique was protein sequencing, and the sequencing of DNA.
- The sequencers showed the nature of a protein/peptide (Aβ) that appeared in the ageing brain, especially in the dementing brain
- They went on to identify that gene that produced an amyloid precursor protein (*APP*) and enzymes that cleaved Aβ from APP.
- They traced the accumulation of Aβ in the dementing brain, as cognition failed.
- They showed this also in the early-onset dementia cases that had fascinated Alois Alzheimer a century earlier.
- This correlation between the accumulation of Aβ and the breakdown of cognition led them, understandably, to propose that Aβ is toxic to the brain.
- And then to seek ways of preventing its accumulation – in the recent study by developing antibodies to Aβ, which would bind tightly to it; in a form in which Aβ would enter the blood stream and leave the brain.
- Novel, pioneering, insightful; and it didn't work.
- The recent study is not novel. Several of these antibody drugs have been assessed by bodies like the American FDA and the Australian Therapeutic Goods Administration. There is now a spirited debate, at least 5 years old, about whether these drugs have failed or are a 'promising starting point for more efforts to treat dementia by extracting Aβ from the brain'.
- There had been frustration in this field for 30 years – perhaps the bodies considering these drugs felt, with some understandable justification – that even this slight benefit might be a starting point for greater success. That's where this last study – the one we began with – comes in.

So something went wrong.

- An evolutionary biologist might have rebuked scientists like myself in a different way:
- How can you just postulate that Aβ, which is produced by the stressed brain is toxic to itself?
- A tenet of evolutionary understanding is that tissues can develop to express novel molecules, but that expression persists in the genome only if it benefits the survival of the species. Why would a self-toxic molecule, as Aβ was assumed to be, ever have evolved?
- And when we dived into the literature on this point, there was evidence that Aβ is trophic to neurones, not toxic; and it counters the toxicity of haemoglobin in cerebral bleeds and acts to prevent opportunistic pathogens getting into the brain – we are just now learning that anti-viral treatment, like the shingles vaccination, is protective against dementia.
- Researchers are now building the list of stress-induced protective molecules produced by the ageing brain – an evolved response to the stresses of aging (which constitute another story – not just Aβ but haemopexin, haptoglobin and the heat shock proteins.
- All this was set aside by the enthusiasm for the molecular genetics, and neglect of the old truth – that a man is old as his arteries.
- The first responder story is of course a hopeful one, some counter the bleakness of the idea that dementia is our fate, escapable only if we die of something else.
- There are many humbling lessons in a story like this.

Finally, before I finish, let's have a quick look at the neuropathology that was so misinterpreted by so many.

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Microvascular pathology in the aging human brain: Evidence that senile plaques are sites of microhaemorrhages

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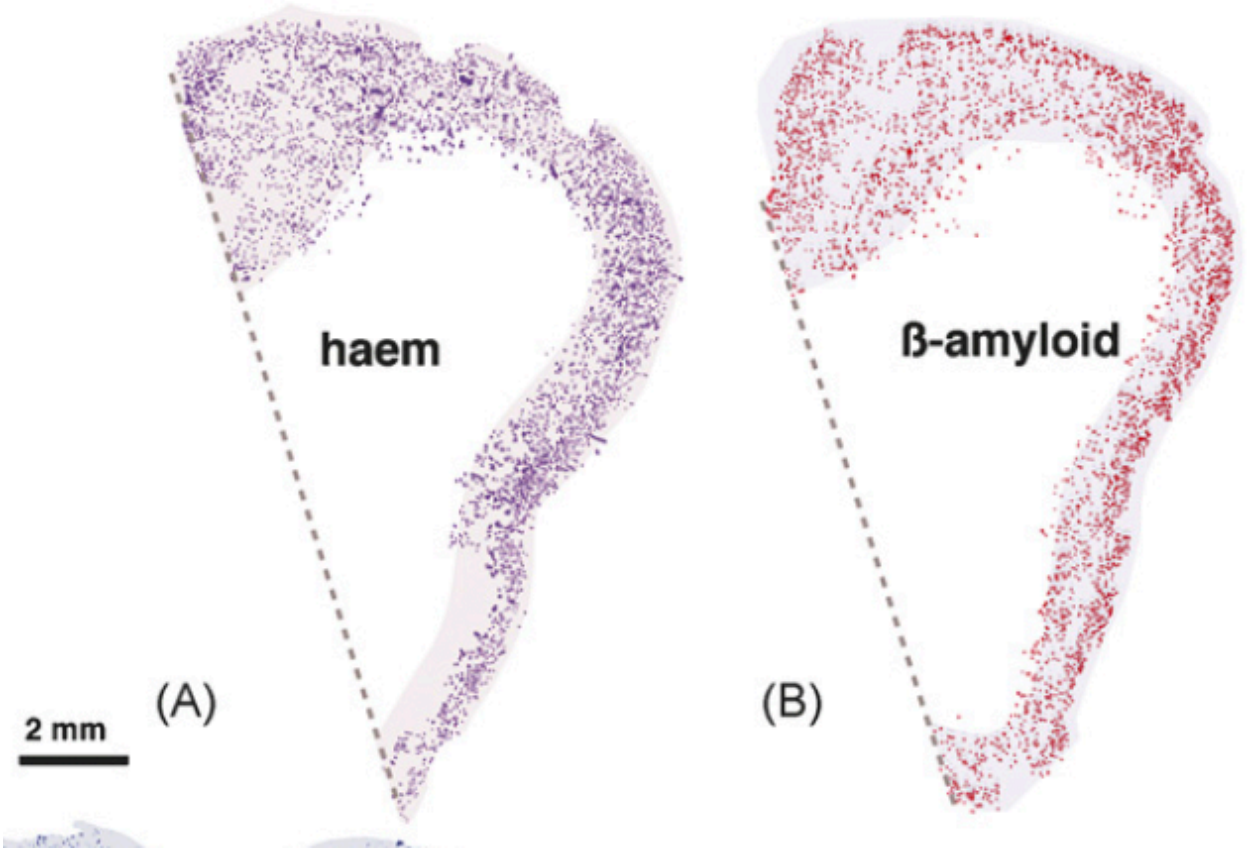
Abstract

Amyloid-rich plaques are a feature of the aging human cerebral cortex. We have recently described another feature of aging human cortex, microhaemorrhages, identified by their content of haem, red blood cells, collagen and clotting factors, and their spatial relationship to capillaries. Here we relate microhaemorrhages to amyloid deposits. Observations were made in three groups: patients with no history of dementia, patients with Alzheimer's disease (AD) and patients with Down's syndrome (DS) and dementia. Amyloid deposits and microhaemorrhages were labelled in adjacent sections, amyloid deposits with antibodies to β-amyloid (βA), and microhaemorrhages by Prussian blue histochemistry for haem. The densities and sizes of βA deposits and haem-rich deposits (HRDs), and their relationship to blood vessels, were surveyed in temporal, cingulate and superior frontal cortex. Our results suggest that HRDs and βA deposits are the same sites of pathology. Their densities in the cortex and white matter of the regions surveyed varied markedly between cases, particularly between demented and non-demented cases, but they always co-varied; where haem deposits were sparse or numerous, so were βA deposits. Both HRDs and βA deposits formed adjacent to or encircling small vessels, often at branch points, and a spatial proximity analysis confirmed that both were found close to or colocalising with microvessels. Both HRDs and βA deposits were associated with blood- or vessel-derived proteins (fibrinogen, von Willebrand factor

Using modern microscopy and molecule-specific markers, the dementing human brain shows:

- Spots of Aβ (pink, at left)
- Spots of bleeding (violet, left).
- Neither is there in the young brain
- Aβ+ plaques form where there is a small (capillary) bleed.
- The cause of dementia is this spotty bleeding – so it is a vascular disease.
- All sorts of implications



At very high power, each Aβ+ spot is a small ‘explosion’ near a tiny vessel.

Each plaque is a site of a small haemorrhage.

The cumulative effects …… dementia.

Remember: the Aβ is a protective molecule secreted by nearby nerve cells.

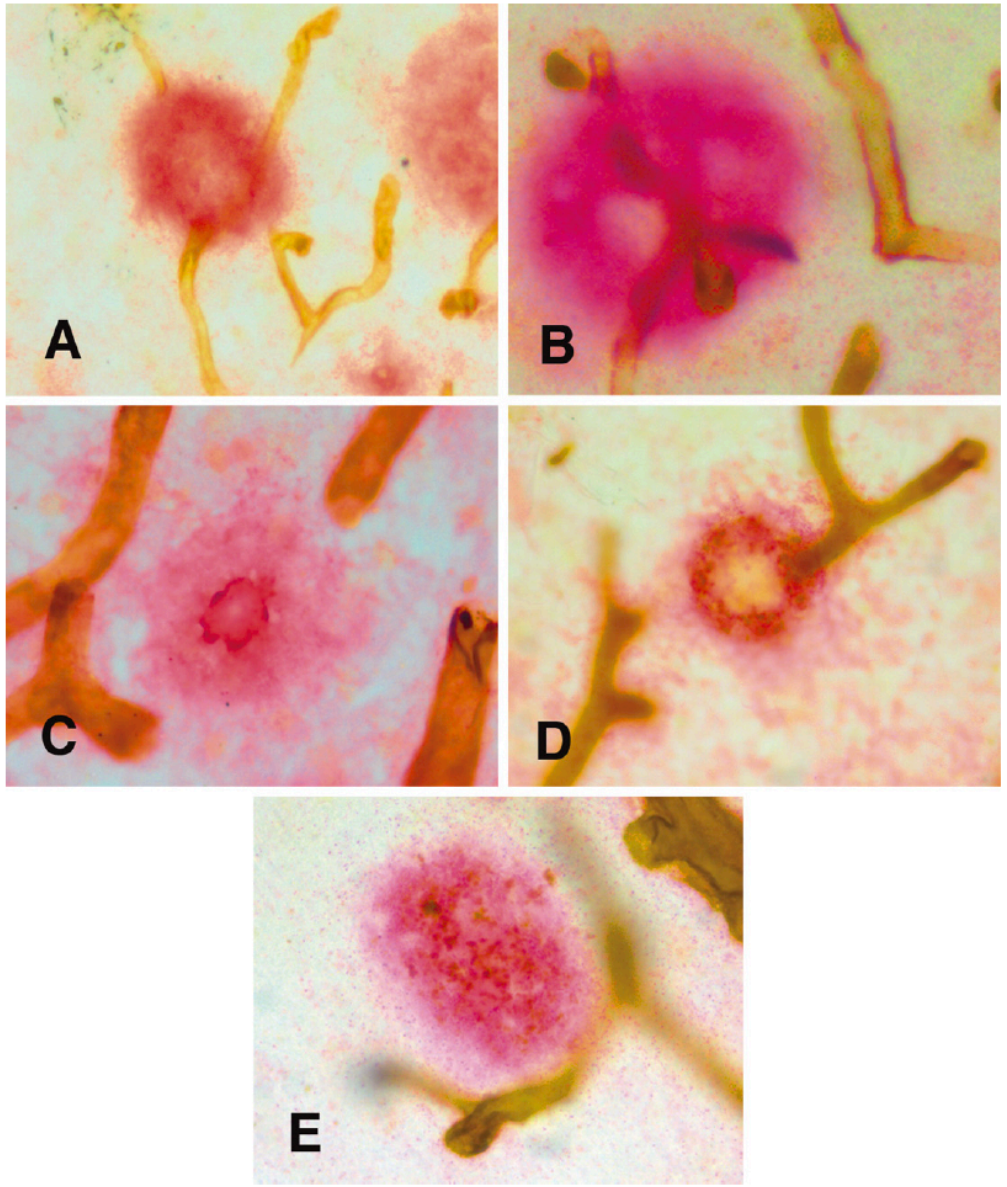


Fig. 7. Colocalisation of βA and collagen. The collagen label shows vessels, but also shows less structured labelling within βA deposits. This colocalisation is of interest because collagen is present in the brain only in association with endothelial basement membrane. Scale bar = 50 μm for (A–F). (A) Vessels passing through a βA deposit (Case AD10). (B) Vessels within a βA deposit (Case DS2). (C and D) Vessels circle and converge on these βA deposits. Diffuse collagen labelling is apparent within the deposit in (D) (superior frontal cortex, AD1 and AD9). (E) This deposit is adjacent to a capillary branch point and contains distinct collagen-labelled debris (Case AD6 subiculum).

SUMMARY

- Dementia is known from the oldest records of human life
- Many ancient writers considered senility the last, late stage of human life.
- Which you could avoid by dying young.
- In the early centuries of human medicine, dementia and other aspects of aging, were understood as the result of vascular pathology – *a man is as old as his arteries.*
- With modern techniques of sequencing of proteins and genes, a new idea became widespread in the late 20th Century- the amyloid cascade hypothesis – that dementia is driven by the accumulation in the brain of a toxic peptide secreted by stressed nerve cells – Aβ.
- The evidence supporting the ACH has stood the test of time – except for 1) its assumption that Aβ is toxic and 2) for the empirical disappointment that clearing Aβ out of the brain does not – our starting point – provide clinical benefit.
- Other scientists have updated the vascular dysfunction idea – localising the driving pathology to capillary dysfunction, in my view capillary haemorrhage.
- The evidence supporting microhaemorrhage as causal has been developed for late-onset dementia (Alzheimer's), early onset dementia (familial), for dementia pugilistica, for trauma-accelerated dementias (CTE) and more.
- Nearly 3 decades ago, investigators began to ask whether Aβ is really toxic?– or may be protective, a first-responder molecule? The evidence for this latter idea is growing.
- And finally giving some hope for how we can fend off the tragedy of dementia.
- Nobody should object to debate among scientists – it is healthy, creative. But do medical researchers have an additional duty? To respond more quickly to new ideas – to limit the suffering of patients and their carers?

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