Insight

Re-aligning scientific and lay narratives of Alzheimer's disease

For the **biological definition of Alzheimer's disease** see *Alzheimers Dement* 2018; **14:** 535–62

For more on **brain amyloidosis in dementia** see *JAMA* 2015; **313:** 1939–49

For more on a **non-scientific narrative of Alzheimer's disease** see Block SM. A Place Beyond Words: The Literature of Alzheimer's. *The New Yorker*, August 20, 2014

For more on the **new research framework** see *Alzheimers Dement* 2018; **14:** 532–34

For the **WHO definition of risk factor** see https://www.who.int/topics/risk_factors/en

It is unsettling to realise that Amazon's best-selling books on Alzheimer's disease claim that scientists have so far got it all wrong, and that the disease can be reversed with appropriate nutrients and lifestyle changes. In March 2019, the number one hit of a Google image search for "top world Alzheimer's physicians" was the cover of a book with similar claims. Others go even further and suggest that Alzheimer's disease is a medical construct artfully devised to expand the drug market. With evident disregard for the many clinical trials of symptomatic treatments, the French national health agency has withdrawn reimbursement of dementia drugs and forbidden producers of amyloid positron emission tomography (PET) tracers to sell their regulatory approved products in the country. Some practitioners claim that the diagnostic workup of academic memory clinics, consisting of imaging and CSF biomarkers, is but an expensive intellectual exercise, as it is not actionable (ie, followed by effective interventions). In these circumstances, we argue that the disease narratives of scientists and society are increasingly divergent and that the scientific community should become aware of the divide, try to align the two narratives, and progress in synergy with society towards finding a cure.

A substantial body of biological, genetic, and epidemiological evidence indicates that amyloid deposition in the brain (brain amyloidosis) is an early event in the disease course, that amyloid is often followed by aggregation and spread of hyperphosphorylated tau, and that this is followed by synaptic dysfunction, neuronal loss, cognitive dysfunction, and finally progression to dementia. Importantly, the phase when biological events (amyloid and tau deposition) are detectable by imaging or CSF markers in the absence of cognitive dysfunction can last up to 20 years, and 20 to 30% of healthy individuals aged 65 years and over have substantial amounts of amyloid in their brain.

The evidence associating amyloid deposition with adverse cognitive outcomes is mounting, such that scientists have re-conceptualised Alzheimer's disease as a state that comprises primarily brain amyloidosis and tauopathy, irrespective of cognitive symptoms. This operational framework (also known as ATN from the biological markers of amyloidosis, tauopathy, and neurodegeneration) is a key enabler to identify asymptomatic persons who might be on the way to develop dementia and enroll them in clinical trials of anti-amyloid or anti-tau drugs to prevent or delay cognitive impairment. However, this new framework also stipulates that, for instance, a 70-year-old person with no memory symptoms, normal cognitive performance, and no disability, but who has an abnormal PET or CSF amyloid test, is on the Alzheimer's disease continuum. If results are also abnormal on a PET or CSF tau test, they have Alzheimer's disease. The framework has a number of undeniable merits, among which are the focus on the preclinical phase, enabling preventive intervention, the emphasis on multiple pathways to the neurodegenerative dementias, the definition of a common language with which researchers can communicate, the independence from a specific technique to measure biomarkers, and above all the focus on amyloid and tau as major actors in neurodegeneration.

But the language that comes with the new framework should be in tune with the social representation of Alzheimer's disease (figure). In novels, films, and newspapers, Alzheimer's disease is a condition featuring progressive forgetfulness leading to severe loss of self-sufficiency and finally a profoundly disabled and fully dependent state. The authors of the ATN framework responsibly warned that it "should not be used in general medical practice as it is premature and inappropriate", but we are concerned about the real possibility to enforce this cautious policy. The history of another disease for which the scientific and social narratives were aligned from inception, and whose prevention turned out to be one of the major successes of recent medicine, can illustrate what needs to be done in our field (panel).

Are brain amyloid and tau markers of Alzheimer's disease, as the ATN framework stipulates, or risk markers? WHO defines risk factor as "any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease or injury". A number of consequences follow from this definition: (i) the risk factor is neither necessary nor sufficient to bring about the disease or injury

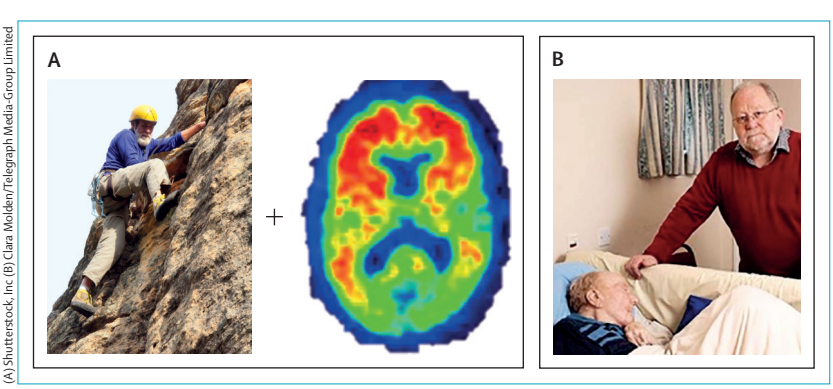

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Figure: **Alzheimer's disease narratives for scientists or society**
To scientists, a fully independent old person with brain amyloidosis is on the Alzheimer's disease continuum. A positive brain amyloid PET scan is shown featuring amyloid deposition in the frontal and parietal cortex of a fictitious elderly person who is an accomplished climber (A).To society, Alzheimer's disease denotes a dreaded incurable condition leading invariably to profound disability and loss of personal dignity (B).

(a corollary being that the disease or injury can develop also in the absence of the risk factor); (ii) the disease can be promoted by other risk factors or combinations thereof; and (iii) a mechanistic relationship should be demonstrated between the risk factor and the disease (eg, via therapeutic modulation followed by risk reduction). Hypertension satisfies all of the above criteria and interventions to control hypertension are effective in prevention of cardiovascular disease.

Hypertension is currently regarded as a disease in itself when malignant or if associated with target organ damage, featuring under at least four diagnostic codes in the ICD-11. It did not always used to be like this. Hypertension was absent in the ICD until its 6th revision, developed in 1948. At that time, only malignant hypertension with blood pressure values higher than 210/100 mm Hg was recognised as a disease, while lower levels were referred to as benign hypertension. Benign hypertension ceased to be such only with ICD-9 in 1975, well after the Veterans Administration Cooperative Study (VACS) demonstration of a relationship between blood pressure levels and vascular events. The shift in diagnostic definitions of hypertension mirrors the accumulating evidence for beneficial treatment effects of hypertension at lower blood pressure thresholds, based on numerous clinical trials during the past 50 years.

From the vascular disease story, we can learn that a scientific narrative in which brain amyloidosis is regarded as a risk marker would not prevent research on amyloid lowering agents, nor hamper the development of an effective anti-amyloid treatment for Alzheimer's disease. Nor would it prevent categorisation of individuals based on the combination of risk markers (amyloid only, tau only, both, neither, or any combination of these and other risk markers or disease markers such as neurodegeneration) to elucidate the natural history of different risk groups. In the clinic, it will not prevent the use of combination therapies consisting of anti-amyloid and anti-tau, and others such as anti-alpha synuclein and anti-inflammatory drugs, that might be developed in the future.

Narratives of acceptance of high risk exposures abound in individual and collective mental representations (for instance, familial history of disease, recreational use of alcohol, extreme or high risk sports, etc) and it seems reasonable to predict greater openness to accept the notion of carrying a risk marker, even one for which no treatment is available, than of carrying an untreatable disease.

In conclusion, we propose to refrain from using the Alzheimer's disease label for cognitively intact people showing abnormal amyloid markers (CSF or PET) but normal or unknown tau markers. We propose to call this condition amyloidosis of the brain, and consider it as a risk marker for neurodegenerative dementia. A similar approach can be envisioned for the deposition of hyper-phosphorilated tau without amyloid nor symptoms (tauopathy of the brain).

Panel: A success story to learn from

This is the story of a medical condition (that we will call disease D) responsible for a large share of all-cause mortality in the 20th century. A President of the USA was affected by disease D, which spurred interest and facilitated funding by the National Institutes of Health of the largest ever cohort study on this disease. The study allowed to establish beyond any reasonable doubt that high levels of a continuous physiological measure (that we will call biomarker B) often but not invariably preceded disease D by many years, that people could feature abnormal biomarker B for a long time without ever developing disease D and die of other causes, that disease D was also associated with other conditions and environmental exposures, and that disease D could develop even in the absence of abnormal biomarker B. Abnormal biomarker B was not the only candidate culprit of disease D, but clinical evidence supported the plausibility of a causal association. Nevertheless, a large part of the disease D-research community believed that normalising biomarker B would not treat disease D, and that an effective treatment to disease D could come only from detailed knowledge of its pathophysiology. Another faction of the disease D-research community believed that complete knowledge of the pathophysiology was not mandatory to set up clinical trials to test drugs capable of decreasing the levels of biomarker B in the hope of preventing disease D. The first clinical trial showed that abnormal levels of biomarker B could be decreased with appropriate drugs and consequently the incidence of disease D was greatly reduced.

Despite a number of analogies, disease D is not Alzheimer's disease. Cardiovascular disease was responsible for about 55% of all-cause mortality in the 1950s. The US President is not Ronald Reagan, but Franklin D Roosevelt, who died of intracranial hemorrhage 2 months after the Yalta Conference, with blood pressure raising well above 200/100 mmHg since the D-Day. The cohort study is not ADNI, but the Framingham heart study, funded in 1948 by the National Heart Institute with 500 000 US$ (today's 35·5M US$). Biomarker B is not amyloid but hypertension, and the term risk factor was coined by William B Kannel following the results of the Framingham heart study supporting an association between hypertension and incident vascular disease. The two factions are not baptists and tauists, but vascular experts who believed that decreasing blood pressure amounted to "treating the manometer" and others believing in the causative association between high blood pressure and vascular events. The clinical trial CT is not the one with the AN1792 vaccine, but the 1967 Veterans Administration Cooperative Study (VACS) with hydrochlorothiazide, reserpine, and hydralazine, in which diastolic blood pressure was successfully decreased in severe hypertensives by 28 mm Hg and vascular morbidity and mortality were dramatically decreased. The era of vascular disease prevention was born. Cholesterol-lowering and antidiabetic drugs were developed in the 1970s and 80s, and added to the armamentarium for vascular disease prevention. In 2014, barely 40 years after the original VACS trial, mortality due to heart disease in the USA had decreased by three-fold and mortality due to stroke by eight-fold.

In times of increasing criticism to top-down elitist knowledge, scientists should devote more attention to the societal narrative of this complex disease. We should descend from the ivory tower and ask ourselves the question as to why large and influential segments of society do not share our narrative despite it being based on solid evidence and stringent methodology. Choosing and using words with caution in conversations about Alzheimer's disease is a mandatory first step.

For **Kannel's definition of risk factor** see *Ann Intern Med* 1961; **55:** 33–50

For more on the **treatment of hypertension** see *Front Cardiovasc Med* 2016; **3:** 3

For the **WHO International Statistical Classification of Diseases and Related Health Problems (11th revision)** see https://icd.who.int/browse11/l-m/en

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