The Expected Event

Pavel Kalvach's case that Alzheimer's disease is not a disease: what the human evidence establishes, where the argument fails, and the therapeutic conclusion he declines to draw

Universality · The missing boundary · The mixed brain · The falling toll · The silence about genes · Resilience

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In 2020 a Prague neurologist argued that the disease we have spent a century trying to cure is not a disease at all, but the far tail of a process everyone who lives long enough will traverse. His evidence is almost entirely human and almost entirely population-scale. This paper grades it, finds five of his propositions established and his conclusion unsupported, and recovers the strongest result in his own bibliography — which he cites for something else.

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Abstract

In 2020 an emeritus clinical neurologist in Prague submitted a thirteen-page essay arguing that Alzheimer's disease is not a disease. It is, on his account, the far tail of a lawful and universal process — brain ageing — that every person who lives long enough will traverse; a syndrome assembled out of atrophy, amyloid, tangles, small-vessel disease, white-matter rarefaction and half a dozen other age-related pathologies, none of which is exceptional, and the aggregate of which we have agreed to call by one man's name. *"If its prevalence surpasses 50% by age 85 or 90, it is no more an accident, nor a disease, but an expected event."*

This paper evaluates that argument. It takes it at full strength — the strongest form its author gives it and, in two places, a stronger form than he gives it — and grades it proposition by proposition against the human record, including six years of evidence that postdates his manuscript.

The unusual thing about this argument is its evidence base. It contains almost no mechanism. There is no molecule at its centre, no pathway, no model organism, no proposed intervention. What it has instead is two hundred and eight references, of which the load-bearing ones are population-based autopsy series, community cohorts followed to death, longitudinal psychometrics spanning fifty years, and meta-analyses in the thousands. Judged on the maturity and independence of its evidence it is close to the strongest submission a prize competition of this kind is likely to receive. Judged on mechanistic specificity it is close to the weakest. Almost every scoring system in the field will therefore rank it badly, and this is a fact about the scoring systems.

What the argument establishes. Five propositions survive the test and should be treated as facts about human brain ageing. First, the pathology is nearly everyone's: in 2,332 unselected brains aged 1 to 100, only ten were free of abnormal tau, and β-amyloid plaques rise from 4 per cent of people in their forties to 75 per cent in the tenth decade. Second, no boundary between normal and morbid senescence has been found in any measured domain — psychometric, volumetric, histological, metabolic or vascular — despite fifty years of searching for one. Third, the canonical markers do not track the syndrome they define: amyloid positivity runs at 14–47 per cent among the cognitively intact, and roughly a third of clinically diagnosed patients are amyloid-negative. Fourth, dementia in the community is almost never one pathology: 41 per cent of Alzheimer's dementia is attributable to pathologic Alzheimer's disease, and in the oldest old a person with a single non-Alzheimer pathology is more likely to be demented than a person with Alzheimer pathology alone. Fifth — and this is the result on which his whole case could have rested — the association between Alzheimer pathology and dementia *decays with age* while the association between cortical atrophy and dementia does not. The plaque explains less at ninety-five than at seventy-five; the lost tissue explains just as much.

The fifth of those is in his bibliography and he does not use it. It is reference 69, cited for a claim about regional distribution that the paper does not make. Its actual finding — an

odds ratio for neocortical neuritic plaques falling from 8.63 at age 75 to 2.48 at 95, against 5.11 and 6.10 for neocortical atrophy at the same ages — is the single strongest datum in his own reference list for his own thesis, and it is left on the table. This paper takes it up.

Where the argument fails. It fails at the inference, not at the evidence, and it fails in one place decisively. From *universal* the essay moves to *inevitable*, and from *inevitable* to *not a disease*. The middle step is false. Age-specific dementia incidence in Europe and North America fell by 13 per cent per calendar decade across seven population cohorts and 49,202 people between 1988 and 2015; the Framingham cohort recorded a 44 per cent fall across three decades; English incidence fell about 20 per cent in twenty years; US prevalence at 65 and over fell from 11.6 to 8.8 per cent between 2000 and 2012 while cardiovascular risk in the same population got worse. A toll that falls by an eighth every decade without anyone treating it is not a toll. It is an outcome with causes, and the causes are in the environment. The 2024 Lancet standing Commission puts 45 per cent of dementia within reach of fourteen modifiable factors. Kalvach cites none of this literature — not one secular-trend paper, not one prevention trial.

And there is a silence at the centre of the essay. It contains no discussion of *APP*, *PSEN1*, *PSEN2*, *APOE* or trisomy 21. A theory holding that Alzheimer's disease is what brain ageing looks like at the end must account for the fact that a single inherited mutation produces the identical pathology and the identical syndrome in a brain that is forty-five years old, and that an extra copy of one chromosome produces prodromal disease at a median age of 50.2 years with a symptomatic prevalence approaching 100 per cent by the seventh decade. These are diseases in the plainest sense the word has: exceptional, causally identified, and arriving on a schedule set by a gene rather than by the calendar. The essay's thesis does not survive them, and the essay does not meet them.

The 2021–2026 record cuts both ways, and we decline to round it in either direction. Two anti-amyloid antibodies have now shown, in trials of 1,795 and 1,736 people, that removing the deposit changes the clinical course. That is a causal demonstration of a kind Kalvach's framing predicts you should not obtain from an ageing phenomenon. It is also a demonstration that near-total removal of the defining lesion leaves roughly seven-tenths of the decline in place — which is what a mixed-pathology account predicts and an amyloid-primacy account does not. The trials refute his nosology and vindicate his pathology in the same eighteen months.

The conclusion he declines to draw is the important one. Having argued that the target is ageing rather than a disease, the essay stops. It proposes nothing. Its therapeutic reachability is zero — not because the thesis has no therapeutic content but because its author does not state it. If dementia is the tail of ageing, then the intervention is on the rate of ageing, and geroscience is the field the argument implies: senolytics, which have now reached a first-in-Alzheimer's safety trial; the epigenetic-age literature his own reference 196 belongs to; and, more immediately, the vascular and white-matter axis that is the actual subject of his forty-year laboratory career. That career is the second thing this evaluation recovers. He is not a commentator. He is a

cerebrovascular ultrasonographer with primary data on carotid haemodynamics across the adult lifespan and on vasoreactivity against leukoaraiosis, and a historian of the Prague school that produced Oskar Fischer. The essay reads as a career-summary; it is better read as the last chapter of a specific programme, and the programme's own findings sharpen it.

One of those findings contradicts him, and we report it. Reference 109 — his own 2010 study of sixty subjects — is cited in support of defective cerebrovascular reactivity as an underlying mechanism of white-matter lesions. That study's stated conclusion is that the effect of vasoregulatory capacity on early leukoaraiosis "is minimal," with correlation coefficients of 0.01 and 0.08. The citation is used against the source.

What we propose in place of his conclusion is a reformulation that keeps everything his evidence establishes and discards the step it cannot support: Alzheimer's disease is not a disease *of* ageing but a disease *within* ageing, whose entry is near-universal and whose exit is determined by something else. On that reading the interesting variable is not what starts the process — almost everyone starts it — but what decides whether a person who has started it ever becomes demented. That variable is resilience, it is partly environmental, it is falling in the direction that helps, and it is the only part of this system currently known to be modifiable at population scale.

We close with a graded ledger of twenty-two claims, five conditions that would refute the reformulated thesis, and ten experiments in rank order. The first is one nobody has run: a secular-trend analysis of *pathology* rather than dementia, asking whether the brains of people born in 1940 carry less Alzheimer neuropathologic change at a given age than the brains of people born in 1910. If incidence has fallen by a quarter and the pathology has not, the falling incidence is resilience and not prevention, and every prevention programme in the field is aimed at the wrong endpoint.

Part I — The Argument and the Man

1. The Claim, Stated at Full Strength

It is a discourtesy to evaluate an argument in a weakened form, so we begin by stating this one as its author states it, and in two places more forcefully than he does.

The proposition is that Alzheimer's disease is not a disease. It is the terminal region of a distribution — the distribution of human brain ageing — and the features by which we identify it are the features that everyone who ages far enough acquires. The essay makes this claim in a specific and unusual way, by refusing at the outset to take the disease category as given and asking instead what work the category is doing.

The argument proceeds in five movements.

The semantic movement. What is a disease? The essay opens on the oldest problem in gerontology, the one Blumenthal catalogued as the aging–disease dichotomy: whether senescence is itself pathology, and if not, where the line falls. Kalvach reproduces the positions — that ageing is not sickness in the accepted sense; that the distinction is between programmed and acquired change; that no one dies of old age but always of a disease; that physiological and pathological ageing are so interwoven that separating them is futile — and then applies Strehler's five criteria of ageing (intrinsicality, universality, irreversibility, progressivity, genetic programming) to dementia. His conclusion is that dementia satisfies them. "Being neither removable nor curable it is not a conventional disease, which would 'attack' an otherwise healthy person among his peers." Conventional diseases occur in a minority and are exceptions from normality. Senile dementia, above a certain age, is not.

The statistical movement. This is where the essay's title sentence lives, and it is the load-bearing sentence of the whole argument: "If its prevalence surpasses 50% by age 85 or 90, it is no more an accident, nor a disease, but an expected event. It should be understood rather as an inevitable process, a toll for long life, where the individual has escaped the risks of more severe, namely somatic deadly diseases." Note what this does. It converts a nosological question into an epidemiological one and offers a decision rule: majority behaviour is not pathology. We will test the premise (§13) and the rule (§16) separately, because they fail differently.

The developmental movement. Retrogenesis. Reisberg's observation, replicated across clinical, electrophysiological, histological and neuroimaging modalities, that the losses of dementia run in reverse order to the acquisitions of childhood — that the sixteen stages of Functional Assessment Staging map onto the developmental sequence read backwards, and that the last capacities gained are the first surrendered. Kalvach uses this as evidence of *lawfulness*: a process that

unwinds an ontogeny in order is not an accident befalling a brain, it is that brain running its programme in reverse.

The continuity movement. The longest section of the essay, and the most empirically dense. Kalvach goes domain by domain — psychometric, volumetric, histological, metabolic, vascular, connectomic — asking in each whether a boundary between healthy and diseased senescence can be found. In each he reports that it cannot. Mental capacity declines from the twenties by a single continuous trajectory dominated by processing speed. Brain weight falls from 45–50 years and is 11 per cent below peak by the late eighties. Amyloid deposition is a posttranslational misfolding phenomenon found in 80–100 per cent of the very old. Neurofibrillary change correlates better with cognition than amyloid does, but is itself continuous with age. White-matter rarefaction is present in half to nearly all of the community elderly. Microinfarcts are found in up to 43 per cent of the non-demented. Each domain shows a gradient, and no domain shows a step.

The nosological conclusion. Dementia is a syndrome, not a disease; Alzheimer's disease is an aggregate of neuropathologic changes; and the field's move to define the disease biologically in people who have no symptoms is, on this account, the error made explicit. Kalvach quotes the 2018 NIA-AA research framework approvingly where it says the term refers to an aggregate of neuropathologic changes, and then refuses its central move: "Can not however support the idea, that the whole-life progressing histological changes should be promoted to a 'disease' ignoring absence of its actual clinical manifestation."

Two things are worth noticing before the argument is examined.

The first is that it is a **negative** thesis with a **positive** evidence base. Almost every claim in it is of the form *X does not distinguish the diseased from the aged*. Negative claims of that kind are usually cheap. These are not, because each is carried by a population-scale human study rather than by an inference from a model. The essay's power comes from the fact that it never leaves the human autopsy table or the community cohort.

The second is that it is **not an anti-amyloid paper**, though it is easily mistaken for one. Kalvach's target is not the amyloid cascade; it is the disease category. He is content to let amyloid, tangles, infarcts, white-matter lesions, TDP-43 and Lewy pathology all be real and all be causal. What he denies is that their sum is an entity.

2. The Author: What the Record Actually Shows

The essay reads, at first pass, as the summing-up of a long clinical life — a senior physician's dissent, written from the armchair. That reading is wrong, and correcting it changes how several of the essay's emphases should be understood.

Pavel Kalvach was, at the time of writing, an emeritus neurologist of the Third Faculty of Medicine, Charles University, Prague. The publication record indexed under his name in the biomedical literature runs from the mid-1970s to 2021 and is dominated by one subject: **cerebral haemodynamics measured non-invasively in living people.**

The programme is visible in its primary papers. In 2005 he published a review of cerebral microangiopathy setting out a three-level model of vascular cognitive deterioration — large-vessel occlusion with a single major infarct; middle-calibre vasculopathy with multiple lacunes; and microangiopathy producing leukoaraiosis — and arguing that all three produce cognitive disorder (Kalvach & Gregová, 2004/2005). In 2007 he reported ultrasonographic velocity, pulsatility and resistance measurements in the common, internal and external carotid and vertebral arteries across an age range of 21 to 92, in 199 subjects without stenosis, with two further cohorts of 231 stenotic and 81 recanalised patients — a normative dataset for how the brain's blood supply changes with age (Kalvach et al., 2007). In 2010 his group published transcranial Doppler measurements of vasoregulatory capacity in three age strata, with a separate cohort of forty elderly subjects in whom Fazekas-graded leukoaraiosis was correlated against that capacity (Peisker et al., 2010). And in the same year he published, with Zdeněk Kalvach, a historical study of dementia research in Bohemia and central Europe, tracing the Prague lineage through Redlich, Pick, Kuffner and Oskar Fischer, based on archival material and visits to the nineteenth-century Prague asylums (Kalvach & Kalvach, 2010).

Three consequences follow for how the essay should be read.

First, the white-matter and vascular sections are not a survey. They are his subject. When the essay devotes its longest passages to leukoaraiosis, microinfarcts, hypoperfusion, cerebrovascular reactivity, the neurovascular unit, steal physiology and blood–brain barrier breakdown, it is not padding a general review. It is the author working in his own laboratory's territory, and the density of that material relative to, say, the two paragraphs on inflammation is a signal about where his evidential confidence lies.

Second, the historical passages are primary scholarship. The essay's most striking single move is its quotation of Alzheimer's own doubt, drawn from Fischer's 1912 paper, in which Alzheimer is recorded as saying that druses cannot be considered the cause of a specific classifiable psychosis, that unequivocal *dementia senilis* occurs where druses are not numerous, and that "we must anyway come to the conclusion, that druses are not a producer of senile dementia, but only an accompanying feature of senile involution of the central nervous system." This is not a quotation lifted from a secondary source. It is a man who has published on the archival history of that exact milieu reading the German primary text and translating it. It is also, we note, an argument from authority to the founders — which is a rhetorical move, not an evidential one, and we will not credit it as evidence. But it is correctly sourced, and that is more than can be said for most invocations of Alzheimer's doubts.

Third, and least comfortably: his own primary data are available to test his own claims, and in one place they do not support him. We take that up in §11.

There is a further point about the author that bears on how the argument should be weighted, and it cuts against him. His laboratory published, so far as the indexed record shows, no primary study of dementia cohorts, no autopsy series, no biomarker study and no clinical trial. The essay's evidence is therefore almost entirely other people's, assembled by a reader of unusual breadth. That is a legitimate way to make an argument — synthesis is a form of work — but it means the essay cannot be treated as reporting a research programme in dementia. It reports a *reading* of one.

3. What Kind of Claim This Is

Most theories of Alzheimer's disease propose a mechanism and are judged by whether the mechanism is right. This one proposes a **category error** and must be judged differently. It is useful to be explicit about the difference, because the failure to be explicit about it is why arguments of this kind are systematically mis-scored.

A mechanistic claim says: *the disease is caused by X*. It is tested by manipulating X. It has a natural therapeutic reading — remove X — and therefore scores well on any axis that asks what the theory tells you to do.

A nosological claim says: *there is no such thing as the disease you are trying to explain, or there is, but not the thing you think*. It cannot be tested by manipulating anything, because it is not about a cause; it is about whether the explanandum is well formed. Its evidence is distributional: prevalence, continuity, overlap, the failure of proposed boundaries to hold. And it has no natural therapeutic reading at all, which is why on any actionability axis it scores zero by construction.

The two kinds of claim are not in competition and they are not commensurable. A mechanistic theory can be entirely correct about a process and still be about a category that does not carve nature at a joint. A nosological argument can be entirely correct about the category and tell you nothing whatever about what to do on Monday morning.

This has a practical consequence that we state plainly, because it is the reason this evaluation exists. **Any scoring system that assigns weight to mechanistic specificity and therapeutic actionability will rank a strong nosological argument near the bottom of the field, no matter how good its evidence is.** The failure is in the instrument. The correct response is not to inflate the nosological argument's mechanism score — it has no mechanism — but to score evidence and inference separately from mechanism and reachability, and to read the resulting profile as a description of what kind of contribution the work is.

Kalvach's profile on such a reading is unusual and worth stating: near-maximal on the maturity and independence of his evidence, high on the coverage of the phenomenology, and zero on reachability. It is the profile of a strong observation with no exit.

4. The Five Pillars, and What Each Would Take to Break

Before turning to the evidence we fix, in advance, what would count against each pillar. This is done here rather than after the evidence is presented, so that the reader can check that the tests were not drawn around results already in hand.

Pillar One — Universality. *Claim:* the pathology is present in effectively everyone who reaches old age. *Broken if:* a substantial fraction of the very old are found free of Alzheimer-type neuropathologic change on adequate sampling with modern methods.

Pillar Two — Continuity. *Claim:* no boundary exists between normal and morbid senescence in any measured domain. *Broken if:* any variable is found with a bimodal or step distribution separating the demented from the non-demented independent of the diagnosis used to define them.

Pillar Three — Marker failure. *Claim:* the canonical markers do not track the syndrome. *Broken if:* amyloid or tau burden is shown to predict cognition with the accuracy a defining lesion requires.

Pillar Four — Mixed pathology. *Claim:* dementia in the community is the sum of several age-related pathologies, of which Alzheimer's is one. *Broken if:* pure Alzheimer pathology accounts for the large majority of dementia when a full panel is scored.

Pillar Five — Inevitability. *Claim:* the process is a lawful, unavoidable toll of long life. *Broken if:* age-specific incidence is shown to vary with time, place or intervention.

We will find that Pillars One through Four survive, three of them decisively, and that Pillar Five fails outright — and that the essay's nosological conclusion depends on Pillar Five and not on the other four.

5. The Evidence Base: What Two Hundred and Eight References Are Made Of

The bibliography is worth characterising, because it is the essay's principal asset and its principal limitation.

By type, the references divide roughly as follows. About a quarter are population-based or community-based human studies — autopsy series, longitudinal cohorts, epidemiological surveys. About a fifth are neuroimaging studies, weighted heavily toward MRI volumetry, diffusion imaging and amyloid or tau PET. About a sixth are neuropsychological, and this set is deep in a way that is rare in this literature: Wechsler, Hebb, Atkinson and Shiffrin, Baddeley and Hitch, Norman and Shallice, Schaie's Seattle Longitudinal Study, Salthouse and Kail on processing speed, Graf on implicit versus explicit memory, Rönnlund on episodic versus semantic trajectories. About a tenth are vascular and cerebrovascular, including four of his own. A handful are historical primary sources in German from 1900 to 1912. The remainder are mechanism papers — tau phosphorylation, mitochondrial dysfunction, oxidative stress, protein misfolding, prion biology — and these are the weakest part of the list, cited briefly and without evident engagement.

Three properties follow.

The evidence is human. There is essentially no animal work in the load-bearing sections; the rodent ischaemia papers in the vascular section are the exception, and they are used to support a claim (that ischaemia produces Alzheimer-type histology) that is doing real work in the argument and rests on models. That is a weak point and we return to it.

The evidence is old, and this is not a criticism except in one place. A bibliography of 2020 whose median date is around 2010 is appropriate for a thesis about lawfulness across the lifespan: the observations he needs are stable ones, made repeatedly since the 1960s, and their age is a mark of replication. The exception, and it is fatal to Pillar Five, is that a thesis about the inevitability of an age-related outcome must engage the literature on whether the age-specific rate of that outcome is changing. That literature existed in 2020, was prominent, and is absent.

The evidence is not adversarial. With one partial exception — the balanced handling of the tau-before-amyloid versus amyloid-before-tau dispute — the essay does not present the strongest case against itself. There is no section on autosomal-dominant disease, none on Down syndrome,

none on the prevention trials, none on the secular trend. An argument that omits its four best counter-examples has not been stress-tested by its author, and the burden of doing so falls to the reader.

We now take up that burden, beginning with what survives.

Part II — What the Argument Establishes

6. Almost Everyone Ignites

The first pillar is the strongest, and the decisive evidence for it is in Kalvach's own bibliography.

Braak, Thal, Ghebremedhin and Del Tredici examined 2,332 unselected brains from individuals aged 1 to 100 years, using AT8 immunocytochemistry and Gallyas silver for abnormal tau and 4G8 with Campbell–Switzer staining for β-amyloid (Braak et al., 2011). Three numbers from that study bear on the present argument, and Kalvach uses only one of them.

The number he uses is the amyloid trajectory: plaques appear in the forties in about 4 per cent of cases and culminate in the tenth decade at 75 per cent. He cites it correctly.

The two he does not use are more important for his case. The first is the denominator of tau: of the 342 cases negative on Gallyas silver, restaining with AT8 left **only ten immunonegative out of 2,332** — that is, abnormal tau protein was detectable in about 99.6 per cent of the brains examined, at every age from childhood upward. The second is the distribution of the earliest change: **fifty-eight cases carried abnormal tau confined to subcortical sites, predominantly the locus coeruleus, with no abnormal cortical tau at all.**

Put together, these say that the initiating lesion of the disease is present in effectively the entire population, that it appears early, and that in a substantial subset it never leaves the brainstem. That is Pillar One, stated more strongly than Kalvach states it, from a paper he cites for something else.

The corollary is arithmetic and it is severe. If the entry event is present in 99.6 per cent of people, then it is not a *risk factor* for dementia in any useful sense. A variable that everyone has cannot discriminate between those who develop an outcome and those who do not. Whatever explains why one person in ten becomes demented and nine do not, it is not the presence of the initiating pathology, because both groups have it.

This point has a formal name that the field has partly adopted since Kalvach wrote. Primary age-related tauopathy — tau in the medial temporal and brainstem distribution, without appreciable amyloid — was formalised as a category by Crary and colleagues in 2014 precisely to accommodate the observation that this pathology is a common finding in human ageing (Crary et al., 2014). Its frequency is very high: in a forensic series of 1,589 autopsies aged 40 and over, 45.2 per cent met criteria for PART, with prevalence peaking at 65.5 per cent in the seventh decade (Yoshida et al., 2024). Its dementia yield is low: in The 90+ Study, participants with PART had dementia at 21.7 per cent, against 50 per cent for Alzheimer neuropathologic change (Leiby et al., 2023).

We flag one thing about PART that neither Kalvach nor its proponents dwell on, and that cuts in his favour. A category created to describe pathology that is common, age-related and mostly non-dementing is, definitionally, a category created to remove from the disease the part of the disease that everyone has. Whether that is a discovery or a bookkeeping operation is exactly the question Kalvach is asking.

Grade: Established. Human, population-scale, replicated, and stronger than the essay claims.

7. No Boundary Has Been Found

The second pillar asserts a negative, and negatives are hard. What makes this one credible is the number of independent instruments that have been pointed at the question and failed to find a line.

Psychometrics. Kalvach's treatment here is his best writing, and it rests on a literature most mechanistic accounts of this disease never touch. Wechsler's 1958 statement is quoted in full: that from Galton onward, nearly every study of the age factor in adult performance has shown that measurable human abilities decline progressively after a peak between 18 and 25, and that the decline occurs in *all* mental measures. Schaie's Seattle Longitudinal Study, testing at seven-year intervals, found perceptual speed declining most linearly and earliest, from about 25; crystallised abilities such as vocabulary holding or rising until 55–60 and only then falling. Salthouse's analysis of the discrepancy between cross-sectional and longitudinal estimates concluded that longitudinal designs *mask* decline through retest effects, and that when this is corrected, some aspects of age-related cognitive decline begin in healthy educated adults in their twenties and thirties (Salthouse, 2009).

That last finding deserves emphasis, because it is the psychometric equivalent of the Braak result. If measurable decline begins in the third decade in healthy people, there is no candidate onset age for a disease process that is not also the onset age of ordinary adulthood.

Volumetrics. Brain weight peaks around 19, begins falling at 45–50, and is about 11 per cent below peak after 86. A meta-analysis of 56 longitudinal MRI studies in 2,211 participants aged 4 to 88 found steady volume loss of 0.2 per cent per year accelerating to 0.5 per cent around 60 and more steeply thereafter. Annual atrophy rates of 0.79–2.0 per cent for hippocampus and 0.3–2.4 per cent for entorhinal cortex are reported in the non-demented. Kalvach's own summary of the comparison — 0.45 per cent per year in non-demented versus 0.98 per cent in demented people — is the shape of the whole problem in one line: a factor of two between groups, on a variable that is changing in both.

Histology. Amyloidosis in autopsy series reaches 80–100 per cent prevalence at advanced age. Neurofibrillary change is universal in the sense established above.

Vascular. White-matter hyperintensities are found in 50–98 per cent of general elderly community samples, in 67–98 per cent of stroke patients, in 28.9–100 per cent of people labelled with Alzheimer's disease, and in 30–55 per cent of Parkinson's patients — a range whose most striking feature is how badly the labels separate. Microinfarcts occur in 3–43 per cent of the non-demented across twelve studies of 1,229 people aged 70–95.

Each of these is a gradient. None is a step. Fifty years of instrumentation improvements have not produced a bimodal distribution in any domain.

One honest qualification. The absence of a boundary in *measured* variables is not proof that no boundary exists; it is compatible with a threshold effect on an unmeasured variable, or with a boundary in rate rather than level. The strongest form of the continuity argument would require showing that no transformation of the measured variables yields separation, and that has not been shown. What has been shown is that the natural candidates do not separate, repeatedly, across instruments that have no reason to fail in the same direction.

Grade: Established, with the qualification stated.

8. The Marker That Does Not Track

Pillar Three is the most familiar of Kalvach's claims and the one where the essay's assembly of the literature is most efficient.

Among cognitively well-preserved individuals, amyloid PET positivity is reported between 14 and 47 per cent across eight studies. Conversely, among people carrying a clinical diagnosis of Alzheimer's disease, amyloid PET is negative in about 32 per cent. A meta-analysis of 64 studies representing 7,140 subjects found that working memory, processing speed, visuospatial function and semantic memory bore no significant relationship to amyloid burden; only episodic memory did.

The essay draws the right conclusion and does not overdraw it: the link between amyloid and mental performance "appears to be unreliable." It does not claim that amyloid is inert, and it explicitly grants that higher amyloid stages associate with faster cognitive decline and with atrophy.

There is a second-order point here that Kalvach makes in passing and that is worth extracting, because it is a methodological observation about the whole field. Once a biomarker is used to *define* the disease, its correlation with the clinical syndrome stops being an empirical finding and becomes a definitional one. If Alzheimer's disease is amyloid-positive by definition, then the 32 per cent of clinically diagnosed patients who are amyloid-negative do not have the disease — and the correlation between amyloid and dementia has been improved by fiat. Every biological-definition framework has this property. It is not a flaw that can be fixed by better biomarkers; it is a consequence of using a marker for both definition and test.

Grade: Established.

9. Almost Nobody Has One Pathology

Pillar Four is the one where the evidence has moved furthest since 2020, and it has moved in Kalvach's favour.

The arithmetic he cites is Boyle's. In 1,161 participants from two clinical–pathological cohort studies of ageing, 512 (44.1 per cent) had Alzheimer's dementia at death. Modelling eight neuropathological indices, **41.0 per cent of Alzheimer's dementia cases were attributable to pathologic Alzheimer's disease.** The remainder was distributed across macroscopic infarcts (8.9 per cent), Lewy bodies (10.8 per cent), hippocampal sclerosis (5.2 per cent), TDP-43 (11.7 per cent), cerebral amyloid angiopathy (8.1 per cent), atherosclerosis (6.0 per cent) and arteriolosclerosis (5.2 per cent). All eight together accounted for 83.3 per cent, falling to 67.5 per cent after adjustment for cases driven by other factors (Boyle et al., 2019).

Two implications, and the second is the one usually missed.

The first is the headline: the disease that gives the syndrome its name accounts for two-fifths of it.

The second is the residual. After eight age-related pathologies are scored, **about a third of Alzheimer's dementia remains unattributable to any of them.** This is not a small correction. It means that the pathologies we can see, taken all together, leave a third of the outcome unexplained — and that a third of the people who die with the clinical picture of Alzheimer's dementia have brains in which no known lesion accounts for it. Whatever is going on in those brains is invisible to a full modern neuropathological panel.

The Kawas data from The 90+ Study sharpen this into something more surprising. Among 183 autopsied participants with longitudinal follow-up, multiple pathological diagnoses were present in 45 per cent of the demented against 14 per cent of the non-demented. Participants with intermediate or high Alzheimer pathology *alone* were three and a half times more likely to be demented; participants with a single **non-Alzheimer** pathology were **twelve times** more likely (Kawas et al., 2015). In the oldest old, having only Alzheimer's disease is a comparatively good position to be in.

That result is a genuine problem for any framework that treats Alzheimer pathology as the principal driver of late-life dementia, and it is a genuine support for Kalvach's contention that the label has been attached to the wrong object. In the age band where most dementia actually occurs, the eponymous pathology is neither necessary, nor sufficient, nor the most dangerous single finding.

Grade: Established, and stronger in 2026 than in 2020.

10. The Result He Left on the Table

Now the observation this evaluation exists to recover.

Reference 69 of the essay is Savva and colleagues, *Age, neuropathology, and dementia*, from the Medical Research Council Cognitive Function and Ageing Study — 456 brains from people aged 69 to 103 at death, assessed by a standard protocol covering Alzheimer pathology, cerebral atrophy and cerebrovascular disease (Savva et al., 2009). Kalvach cites it for a claim about regional distribution: that amyloid increases first in neocortical and later in allocortical regions up to 75 years and remains stable in the oldest old. That claim is not what the paper reports.

What the paper reports is this. The association between neocortical neuritic plaques and dementia was **strong at age 75 (odds ratio 8.63, 95% CI 3.81–19.60) and reduced at age 95 (odds ratio 2.48, 95% CI 0.92–4.14)** — the confidence interval at 95 crossing unity. Similar attenuations with advancing age were observed for the other Alzheimer-type changes in all brain areas. But **neocortical cerebral atrophy maintained its relationship: odds ratio 5.11 (1.94–13.46) at 75 and 6.10 (2.80–13.28) at 95.**

Read that again in the terms of Kalvach's own thesis. As people get older, the pathology stops explaining who is demented — and the *tissue loss* keeps explaining it, undiminished. The plaque is losing its grip on the outcome at exactly the ages where most dementia occurs. The atrophy is not.

This is the strongest single result in his bibliography for his own case, and it is stronger than anything he actually argues from, for three reasons.

It is a within-study interaction, not a between-study comparison. The attenuation is measured inside one cohort with one protocol, which removes the objection that different series score pathology differently.

It dissociates two things his opponents run together. "Alzheimer's disease" as a pathological entity and "neurodegeneration" as tissue loss are usually treated as the same claim at different resolutions. Savva separates them and finds they behave differently with age.

It supplies the missing variable. Kalvach's essay is repeatedly forced to say that something other than plaques and tangles determines the outcome, and repeatedly declines to name it. Savva names it: cortical atrophy. Not as a mechanism — atrophy is an outcome, not a cause — but as the level of description at which the association with dementia survives ageing.

Why the essay missed it we cannot know. The most likely explanation is mundane: the paper was read for its amyloid-distribution content, catalogued under amyloid, and never revisited. But the effect is that the argument's best evidence sits unused fifteen references before its conclusion.

Grade: Established, and unclaimed by its author.

11. The White Matter — and the Place Where His Own Data Disagree

Kalvach's vascular sections are the essay's densest and, given his career, its most authoritative. They are also where we must record a citation used against its source.

The case he assembles is this. Atherosclerotic deterioration in large and small vessels degrades circulatory efficiency, pulsatility and haemodynamic adaptability. The underlying mechanisms are hypoperfusion and defective cerebrovascular reactivity. Small-vessel disease manifests in two forms: microinfarcts, found in border zones and therefore of hypoperfusion aetiology, present in 3–43 per cent of the non-demented and 20–100 per cent of people with Alzheimer's disease, and in whole-brain terms plausibly numbering in the hundreds or thousands given the limited sampling of standard neuropathology; and white-matter lesions producing leukoaraiosis, whose progression parallels cognitive decline most intensively in processing speed and executive function. Blood–brain barrier breakdown is documented as an early biomarker of human cognitive dysfunction independent of amyloid and tau status (Nation et al., 2019). And in non-human primates, where tissue can be examined immediately after death, white matter deteriorates more markedly than grey.

The convergence with his psychometric section is the strongest structural argument in the essay and he does not quite make it explicit, so we will. **The earliest and most linear psychometric decline is in processing speed. The pathology that damages processing speed most specifically is white-matter disease. White-matter disease begins in the fifth decade and progresses with age in nearly everyone.** Three independent literatures — neuropsychological, imaging and neuropathological — pick out the same axis, and it is not the axis the disease category is built on. The disease category is built on episodic memory and the medial temporal lobe. That is a real and under-argued point, and it is available to him.

Now the problem.

The essay writes: "The underlying neuropathological mechanisms are hypoperfusion (107) and defective cerebrovascular reactivity (108,109)." Reference 109 is Peisker, Bartoš, Škoda, Ibrahim and Kalvach, *Impact of aging on cerebral vasoregulation and parenchymal integrity* — his own paper. That study measured middle cerebral artery flow velocity at rest, after apnoea and after hyperventilation in three age strata, and in a separate cohort of forty elderly subjects correlated Fazekas-graded leukoaraiosis against vasoregulatory capacity. Its findings: mean flow velocity fell with age (71 cm/s in the young to 44.9 in the old); post-apnoeic vasodilatory reserve fell from 41.7 per cent to 32.9 per

cent; hyperventilatory deceleration fell from 50.2 per cent to 29.7 per cent. And then: the correlation of periventricular and deep white-matter lesions was highest with the index of resistance at 0.45, "while with the apnoic acceleration and hyperventilatory deceleration it was minimal (0.01 and 0.08 respectively)." The paper's stated conclusion is that vasoregulatory capacity declines with age and that "its effect on the initial stages of leukoaraiosis is minimal" (Peisker et al., 2010).

The essay cites this paper as evidence that defective cerebrovascular reactivity is an underlying mechanism of white-matter lesions. The paper concludes that it is not — at least not at the initial stages, which are the stages that matter for an argument about how the process begins.

We do not read this as misconduct. It reads as a reference dropped into a supporting cluster from memory of its subject rather than its result, which is among the commonest errors in review writing and one this literature is full of. But it has a substantive consequence that should be recorded rather than smoothed over: **the essay's proposed mechanism for its own strongest axis is the one mechanism its author tested and failed to confirm.** The white-matter case survives — the epidemiology and the correlation with processing speed are not touched by this — but its causal story is weaker than the essay presents, and weaker by the evidence of the author's own laboratory.

There is a second, smaller inconsistency in the same section. At one point the essay states that observing grey and white matter separately shows that thinning "starts in the white matter later"; some pages afterwards it reports primate data showing more pronounced deterioration of white than grey matter, and builds the disconnection argument on white-matter primacy. Onset and magnitude are different quantities and the two statements are not strictly contradictory, but the essay does not distinguish them, and a reader could take away either that white matter goes first or that it goes later.

Grade: Supported for the epidemiology; Contradicted for the proposed mechanism, by the author's own data.

Part III — Where the Argument Fails

12. The Threshold That Is Not Crossed

The essay's nosological conclusion rests on a single quantitative premise: that dementia prevalence "surpasses 50% by age 85 or 90." Everything follows from crossing that line. Below a majority, dementia remains an exception and the ordinary logic of disease applies. Above it, the essay's argument begins.

The premise is not met at either age, and its source will not carry it.

The citation is to Chen and Fernandez, a 2001 commentary in *Frontiers in Bioscience* re-examining the Alzheimer movement twenty-five years on and asking whether the condition is a disease or a senile condition in medical nature. It is a position paper, not a prevalence study. No population estimate originates there.

The population estimates that do exist are as follows. In The 90+ Study, a population-based investigation of 911 people aged 90 and over — the largest series in the relevant age band — overall dementia prevalence was **45 per cent in women (95% CI 41.5–49.0) and 28 per cent in men** (Corrada et al., 2008). At age 90 and above, the whole point at which Kalvach says the majority has been reached, neither sex reaches it, and the pooled figure is well below.

The threshold is eventually crossed, and it is worth being precise about where, because the correct figures make a version of his point better than his own do. Prevalence in that cohort doubled roughly every five years in women. Incidence, measured separately in 330 initially non-demented participants, rose from **12.7 per cent per year at 90–94, to 21.2 per cent at 95–99, to 40.7 per cent per year at 100 and over**, with a doubling time of 5.5 years (Corrada et al., 2010).

That last number is the one Kalvach should have used. An annual incidence of 40.7 per cent means that a non-demented centenarian has, roughly, a coin-flip chance of becoming demented within about eighteen months. Cumulatively, survival to 105 without dementia is close to a statistical curiosity. If the essay's argument is that at some age the outcome ceases to be an accident and becomes an expectation, the evidence supports it — at 100, not at 85.

Why the difference matters is not pedantry. Kalvach's rule is a majority rule, and where the majority sits determines what the rule licenses. At 85 to 90, dementia is a minority outcome in a population where it is common; that is the epidemiological description of a great many diseases, including most cancers and nearly all cardiovascular events. Applying the rule at that age would reclassify half of internal medicine. Applied at 100, the rule identifies a genuinely different regime — but a regime containing a vanishing fraction of the people who actually get dementia, and

therefore a regime that cannot support a general nosological claim about the condition.

Grade of the premise: Contradicted at 85–90 (human, population-scale); Supported at 100+ (human, population-scale, single cohort).

13. The Toll That Is Falling

This is where the argument breaks, and it breaks on evidence the essay does not cite.

The claim under test is that dementia is "an inevitable process, a toll for long life." Inevitability is a strong word and it has a testable consequence: the age-specific rate should be a constant of human biology, not a variable of time and place. It is not.

Framingham. 5,205 participants aged 60 and over under surveillance for incident dementia since 1975, analysed across four epochs with consistent criteria. Five-year age- and sex-adjusted cumulative hazard fell from 3.6 per 100 persons in the late 1970s and early 1980s to 3.0 (hazard reduction 22 per cent), then 2.2 (38 per cent), then 2.0 (**44 per cent**) in the late 2000s and early 2010s. The reduction was seen only among those with at least a high-school diploma (Satizabal et al., 2016).

The Alzheimer Cohorts Consortium. Seven population-based cohorts in the United States and Europe, 49,202 individuals aged over 65, 4,253 incident dementias, 1988 to 2015. Incidence declined by **13 per cent per calendar decade (95% CI 7–19 per cent), consistently across studies**, somewhat more steeply in men (24 per cent) than women (8 per cent) (Wolters et al., 2020).

CFAS I and II. The only multicentre population study designed *a priori* to detect change over time: identical geographical boundaries, identical sampling and approach methods, two decades apart in England and Wales. 5,156 interviewed at baseline in 1989–94, 5,288 in 2008–11. A **20 per cent drop in incidence** (95% CI 0–40 per cent), driven by a reduction in men across all ages above 65 (Matthews et al., 2016).

Health and Retirement Study. Nationally representative US samples of 10,546 and 10,511 individuals aged 65 and over. Dementia prevalence fell from **11.6 per cent in 2000 to 8.8 per cent in 2012** — and did so *despite* a significant age- and sex-adjusted worsening in the cardiovascular risk profile of the same population over the same interval. Rising educational attainment accounted for part of it (Langa et al., 2017).

Four cohorts, two continents, four independent designs, one direction. The age-specific probability that a person becomes demented has been falling for as long as anyone has measured it carefully, in the absence of any effective treatment.

That is not what a toll does. Tolls are collected at a fixed rate. This one has been discounted by roughly a quarter in a generation by forces nobody deliberately applied.

The counter-arguments, taken seriously. Three are worth stating, and none of them saves the inevitability claim.

Diagnostic drift. If criteria or ascertainment changed, apparent incidence could fall without anything real changing. This is why CFAS II matters: it was built specifically to hold method constant, and it still found a fall.

Compression rather than prevention. Falling incidence at a given age could reflect a rightward shift of the same curve — the same lifetime risk, arriving later. This is entirely possible, and it is the most defensible retreat available to the thesis. But note what it concedes: if the curve can be shifted right by education and cardiovascular management, it can be shifted, and a process that can be shifted by external variables is not intrinsic in Strehler's sense. The essay's own criterion is failed.

Stable age-standardised prevalence in global projections. The Global Burden of Disease analysis forecasts 57.4 million cases in 2019 rising to 152.8 million in 2050, with age-standardised both-sex prevalence essentially flat (global change 0.1 per cent) — the increase attributable to population growth and ageing (Nichols et al., 2022). This is often read as contradicting the decline. It does not: it is a global figure dominated by regions where the risk-factor transition is going the other way, and the same analysis identifies scaling up interventions against modifiable risk factors as a principal lever. Flat globally and falling in high-income countries are both true, and the second is the one that tests inevitability.

Grade: Contradicted. Human, population-scale, replicated across four independent designs. This is the finding that breaks Pillar Five, and Pillar Five is what the nosological conclusion rests on.

14. Forty-Five Per Cent

If dementia is a toll for long life, it should not have a large attributable fraction from things people do.

The 2024 report of the Lancet standing Commission on dementia prevention, intervention and care places **around 45 per cent of dementia cases within reach of fourteen modifiable risk factors** across the life course: low education, hearing loss, hypertension, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol, traumatic brain injury, air pollution, social isolation, and — new in this edition — high LDL cholesterol and untreated vision loss, contributing an estimated 7 and 2 per cent respectively (Livingston et al., 2024).

Population attributable fractions of this kind should be handled with care. They assume causality, they assume independence that is not fully warranted, they are computed on risk-factor prevalences that vary by population, and they are not a promise that eliminating the factors would eliminate the cases. Kalvach would be entitled to press all of that. What he is not entitled to do is ignore the trial evidence, which is where an attributable fraction gets tested.

FINGER. A two-year multidomain randomised trial in 1,260 at-risk Finns — diet, exercise, cognitive training and vascular risk monitoring — showing a benefit on a composite neuropsychological test battery (Ngandu et al., 2015).

SPRINT MIND. 9,361 hypertensive adults aged 50 and over randomised to a systolic target below 120 mm Hg or below 140 mm Hg. The trial **missed its primary cognitive outcome**: adjudicated probable dementia, hazard ratio 0.83 (95% CI 0.67–1.04). It hit both secondaries: mild cognitive impairment, HR 0.81 (0.69–0.95), and the composite of MCI or probable dementia, HR 0.85 (0.74–0.97). The parent trial had been stopped early for cardiovascular and mortality benefit, leaving fewer dementia cases than planned; the authors state that the study may have been underpowered for that endpoint (Williamson et al., 2019). We report the primary miss before the secondary hits, because that is the honest ordering.

US POINTER. The largest and most recent: 2,111 participants aged 60–79 at elevated risk, randomised to a structured or a self-guided multidomain lifestyle intervention over two years, with final follow-up in May 2025. The structured arm showed a significantly greater annual rate of improvement in a global cognitive composite of executive function, episodic memory and processing speed — 0.243 versus 0.213 SD per year, difference 0.029 SD (95% CI 0.008–0.050) (Baker et al., 2025).

The POINTER result requires two sentences of honest interpretation, and they pull in opposite directions.

First, the between-arm difference is small — 0.029 SD per year — and both arms were active interventions, so this is not an estimate of the effect of lifestyle change against nothing.

Second, and more interesting for the present argument: **the global cognitive composite went up, in both arms, in people aged 60 to 79 selected for elevated dementia risk, over two years.** Some of that is retest effect — which is exactly the artifact Salthouse identified as masking true decline in longitudinal designs, and which Kalvach's own psychometric section relies on Salthouse to explain. But a lawful, intrinsic, irreversible, progressive process, observed for two years in a 2,111-person cohort enriched for risk, produced a rising line. Whatever else that shows, it does not show a toll being collected on schedule.

Grade: Contradicted for the inevitability claim; Mixed for the strength of the modifiable fraction, which is real but softer than 45 per cent implies.

15. Universality Is Not a Nosological Argument

Here we address the inference itself rather than the evidence, because even if the premise of §12 were met the rule would not license the conclusion.

The essay's rule is: *conditions occurring in a majority of a population are not diseases but expected events.* Applied consistently, this rule produces results nobody accepts.

Presbyopia is universal. Every human eye loses accommodative amplitude on a schedule so regular that it is used to estimate age. It is intrinsic, progressive, irreversible and genetically programmed — Strehler's five criteria, met completely. It is also corrected, at trivial cost, in essentially the entire developed world, and nobody regards the correction as a category error.

Atherosclerosis is present in the majority of Western adults by middle age and in essentially all of the elderly. Its universality did not prevent the identification of modifiable causes, nor the development of statins, nor a halving of age-standardised coronary mortality across four decades.

Osteoporosis, sarcopenia, hearing loss, cataract — the same structure in each case: near-universal at sufficient age, continuous with normal ageing at every measured level, no bimodal boundary, and treated, screened for, and in some cases prevented.

The inference fails because it conflates three distinct properties that the essay treats as one:

- **Universal** — everyone gets it.
- **Inevitable** — nothing can be done about whether you get it.
- **Not a disease** — the disease framework is the wrong tool for it.

Universality entails neither of the others. Presbyopia is universal and inevitable and is nonetheless managed as a clinical condition. Atherosclerosis is near-universal and *not* inevitable and is managed as a disease. Dementia, on the evidence of §13, is near-universal at extreme age and **not inevitable at the ages where most of it occurs** — which places it in the atherosclerosis category, not the presbyopia one.

There is a stronger version of the essay's position that survives this objection, and it is worth constructing on Kalvach's behalf since he does not construct it himself. It is not that universality disqualifies disease status; it is that **the disease framework carries a promise of a discrete**

cause and a discrete remedy, and that promise is unwarranted here, and unwarranted promises misallocate effort. That is a claim about research strategy rather than nosology, it is defensible, and the 2003–2021 record of anti-amyloid failures is evidence for it. But it is not the claim the essay makes, and it does not support the essay's conclusion that the category should be abandoned — only that its promise should be moderated.

Grade of the inference: Fails as stated. A reconstructed version survives and is weaker.

16. The Silence About Genes

The most serious omission in the essay is not an argument it gets wrong. It is a body of evidence it does not mention.

Search the thirteen pages for *APP*, *presenilin*, *PSEN1*, *PSEN2*, *APOE*, *trisomy* or *Down syndrome*. None appears. The word "genetic" occurs in relation to Strehler's criteria and to epigenetic age. The essay's engagement with the genetics of this disease consists of one sentence noting that when age is the main risk factor we must attend to genetic factors causing faster or slower ageing, followed by a citation to a DNA-methylation study of memory maintainers and decliners.

This is a silence at the exact point where the thesis is most exposed, and two literatures fill it.

Autosomal-dominant Alzheimer's disease. Mutations in *APP*, *PSEN1* and *PSEN2* produce, with essentially complete penetrance, the full pathological and clinical picture of Alzheimer's disease at ages between the mid-thirties and the mid-fifties. The Dominantly Inherited Alzheimer Network established the biomarker sequence in 128 participants, indexed to the parent's age at symptom onset: cerebrospinal-fluid Aβ42 declining about **25 years** before expected onset; fibrillar amyloid deposition on Pittsburgh compound B, elevated CSF tau and increased brain atrophy about **15 years** before; cerebral hypometabolism and impaired episodic memory about **10 years** before; global cognitive impairment about **5 years** before; and diagnostic criteria for dementia met at an average of three years *after* the expected onset (Bateman et al., 2012).

Consider what this does to the thesis. A person of 45 with a *PSEN1* mutation has the neuropathology, the syndrome, the biomarker sequence and the clinical course of Alzheimer's disease, in a brain that is by every other measure young. Brain weight is at or near its plateau. Leukoaraiosis is minimal. Perceptual speed is decades from its old-age value. The retrogenesis clock has barely started. Every variable Kalvach identifies as continuous with ageing is at a young-adult value, and the disease is present in full.

Either that person does not have Alzheimer's disease — in which case the essay owes an account of what they do have, and of why it is indistinguishable — or Alzheimer's disease can occur in the absence of brain ageing, in which case it is not the far tail of brain ageing.

Down syndrome. The second case is worse for the thesis because it supplies a dose–response relationship. In 388 adults with Down syndrome studied cross-sectionally against 242 euploid controls, CSF Aβ and plasma neurofilament light change from the third decade of life; amyloid PET in the fourth; FDG-PET and CSF phospho-tau later in the fourth; hippocampal atrophy and

cognitive change in the fifth. **Prodromal Alzheimer's disease was diagnosed at a median age of 50.2 years and Alzheimer's disease dementia at 53.7, with symptomatic prevalence reaching 90–100 per cent in the seventh decade** (Fortea et al., 2020).

Trisomy of chromosome 21 confers a third copy of *APP*. The consequence is the entire disease, in the same order, with the same biomarkers, three decades early, in essentially everyone. That is not brain ageing running to its conclusion; it is a gene-dosage effect on a specific pathway with a specific product, and it is as clean a demonstration of causal sufficiency as human biology offers.

What the essay could have said, and should have. There is a reply available and it is not trivial: that these are *different diseases* which happen to produce a convergent phenotype, and that using them to argue about the sporadic late-life condition is precisely the error the essay is warning against. That reply has real force — the DIAN cohort's biomarker sequence does not match the sporadic sequence in every respect, and Braak's brainstem-first tau ordering in sporadic disease is not what one sees in amyloid-driven familial disease. But the reply must be made, and the essay does not make it. An argument that Alzheimer's disease is not a disease must engage the cases where it demonstrably is one.

Grade: Contradicted. The strongest evidence against the thesis is absent from the document.

17. Nineteen Days

The essay opens with an arresting number, and the number deserves examination because it is doing rhetorical work that its source cannot support.

"The elimination of the main 3 causes of death in the population (cardiovascular disease, stroke and cancer) would result in an increase of only about 15 years and the resolution of Alzheimer's disease (0.7% likelihood of dying from) would add about 19 days onto the average life expectancy."

The competing-risks arithmetic behind this is sound and well established in demography. Cause-deleted life-table calculations do produce modest gains, because removing one cause exposes the population to the others, and because the people saved are old and have high mortality from everything else. Hayflick's *Nature* essay and the Olshansky–Hayflick–Carnes position statement — the essay's references 1 and 2 — make this point about ageing generally. That position statement is, we note, a document written to distinguish the science of ageing from the anti-ageing industry; it is not an analysis of the burden of dementia, and it contains no estimate for Alzheimer's disease.

The argument fails not on its arithmetic but on its choice of outcome. **Life expectancy is a mortality metric, and dementia is a morbidity disease.** Its cost is not measured in the days it removes from the end of life; it is measured in the years of dependence, institutionalisation, lost autonomy and caregiver burden it inserts before that end. A condition that removes almost no lifespan and a great deal of life is the paradigm case for which morbidity metrics were invented.

Worse, the argument boomerangs. If curing Alzheimer's disease would add nineteen days to average lifespan while removing several years of profound dependence for those affected, then it is one of the highest-value targets in medicine on any quality-adjusted measure — because the entire benefit accrues as function rather than as duration, with no offsetting extension of frail life. The nineteen-days figure is the strongest available argument for treating dementia, presented as an argument against taking it seriously.

We think the essay is doing something specific with this number and it is worth naming, because it recurs. It is answering a rhetorical excess with a rhetorical excess. The essay is explicitly annoyed by the field's language — "biggest, relentless killer," "world wide epidemics," "devastating enemy to be eradicated" — and cites discourse-analytic work on how the British press represents dementia and a paper asking whether the war metaphor has exhausted itself. That annoyance is justified; the mortality framing of dementia in public communication is genuinely misleading, and the essay is right that it induces improper fear. But the correct response to a bad mortality claim is not a better mortality claim. It is to point out that mortality is the wrong axis, which the essay is one sentence

away from saying and never says.

Grade: Contradicted as an argument about burden. Correct as an arithmetic observation about life expectancy, and irrelevant to the question it is deployed against.

18. Retrogenesis: Which Half Survives

Kalvach's third pillar is Reisberg's, and it must be split before it can be graded, because the name covers two claims of very different standing.

The clinical claim. That the functional losses of dementia recapitulate in reverse the functional acquisitions of childhood: that continence, ambulation, speech and self-care are surrendered in the inverse of the order they were gained, and that the sixteen stages of Functional Assessment Staging map onto that inverse ordering with correlated changes in activities of daily living, cognition, primitive reflexes and EEG (Reisberg et al., 1999).

This claim is in good health. It is a description of a clinical course, it was derived from clinical observation of large numbers of patients, it has practical value in staging and in care planning, and it does not require any pathogenic commitment at all. Kalvach uses it correctly, as evidence of *lawfulness* — that a process which unwinds an ontogeny in order is not a random accumulation of insults.

The pathogenic claim. That the reason the losses run backwards is that the *last-myelinating* regions are the *first to degenerate* — the "last in, first out" rule that Kalvach states explicitly, citing Fjell: the late-maturing regions are most vulnerable, the predominance of such areas copies the pattern of encephalisation in phylogenesis, rendering them most fragile.

This claim is in poor health, for three reasons that are independent of Alzheimer's disease.

It is two rules wearing one name. "Myelin-based vulnerability" alternates between a **timing** rule (late-myelinating regions fail first) and a **density** rule (poorly myelinated axons are vulnerable as a steady-state property, irrespective of when they myelinated). Across the cortical hierarchy these covary, which is why the conflation survives unnoticed. They are not the same claim, and they dissociate at exactly the places where the rule is being asked to do work.

The classical myelogenetic maps have no entry for the region where cortical Alzheimer pathology begins. The Flechsig-derived maps that the rule depends on chart neocortical areas. Allocortex and transentorhinal cortex — the site of the earliest cortical neurofibrillary change — are not ranked in them. The ordering rule has no rank for the origin.

The rule's most-cited support does not address onset. Braak and Braak's 1996 paper is titled for the neocortex and describes the neocortical spread of neurofibrillary change (roughly Braak stages III–VI), not the origin of the process. It is regularly cited as explaining why the entorhinal cortex goes first. It does not make that claim.

And there is a fourth reason, specific to this disease and decisive if Braak's brainstem-first sequence is accepted. The cortically-projecting neurons of the locus coeruleus — the site where Braak's 2011 series found the earliest abnormal tau, in fifty-eight cases with no cortical involvement at all — are among the earliest-born neurons in the mammalian central nervous system, generated on embryonic day 9 in rodent. On a strict last-in-first-out rule they should degenerate **last**. They appear to degenerate **first**.

So: the clinical half of retrogenesis survives and is useful; the pathogenic half does not survive, and where it makes a prediction about the earliest event, it makes the wrong one.

This matters for Kalvach's argument in a specific way. The clinical half supports *lawfulness* — that the course is orderly — but lawfulness is compatible with disease. Many diseases have orderly courses; that is what staging systems are for. It is the **pathogenic** half that would have supported his stronger claim, that dementia is development running backwards and therefore is development rather than pathology. That half is the one that fails.

Grade: Clinical retrogenesis — Established. Pathogenic retrogenesis — Contradicted.

Part IV — The Test the Argument Was Given

19. The Antibodies: A Test He Did Not Design, and Two Results He Would Read Differently

The essay was written in 2020, months before the first unambiguous demonstration that removing the deposit changes the clinical course. That demonstration is the sharpest available test of a nosological argument of this kind, and it returns two answers that point in opposite directions.

The first answer goes against him.

In CLARITY-AD, 1,795 participants with early Alzheimer's disease and biomarker-confirmed amyloid were randomised to lecanemab or placebo for eighteen months. Change from baseline on the Clinical Dementia Rating–Sum of Boxes was 1.21 with lecanemab against 1.66 with placebo (difference −0.45; 95% CI −0.67 to −0.23; P<0.001), with concordant effects on ADAS-cog14, ADCOMS and the activities-of-daily-living scale, and a between-group amyloid reduction of 59.1 centiloids (van Dyck et al., 2023).

In TRAILBLAZER-ALZ 2, 1,736 participants with amyloid and either low/medium or high tau on PET were randomised to donanemab or placebo for 76 weeks. In the low/medium tau population the integrated Alzheimer's Disease Rating Scale changed by −6.02 with donanemab against −9.27 with placebo (difference 3.25; 95% CI 1.88–4.62), and CDR-SB by 1.20 against 1.88 (difference −0.67). Twenty-three of twenty-four gated outcomes were statistically significant (Sims et al., 2023).

What matters here is not the effect size. It is the *shape* of the inference. Two independent sponsors, two different antibodies, two large randomised trials, one manipulated variable, a dose–response relationship with the biomarker, and a change in the clinical outcome in the predicted direction. That is a causal demonstration in living humans, and it is the kind of demonstration a phenomenon of ageing is not supposed to yield. You cannot randomise people to less senescence and observe a smaller decline. Here that was, in effect, done for one component of the process.

Kalvach's framing predicts that this should not have worked. Amyloid on his account is a posttranslational misfolding phenomenon, near-universal, poorly correlated with cognition, and an accompanying feature of senile involution — Alzheimer's own word, which the essay quotes approvingly. Accompanying features do not, when removed, alter the course of the thing they

accompany. This one did.

The second answer goes with him, and it is the larger of the two.

Take the lecanemab result at face value. Removing enough amyloid to shift the population across the positivity threshold produced a 27 per cent relative slowing of decline on CDR-SB. **Seventy-three per cent of the decline continued.** Donanemab in its best-case stratum — participants pre-selected for low or medium tau, which is to say pre-selected for the earliest and most tractable disease — produced about 35 per cent. **Sixty-five per cent of the decline continued.**

So: the defining lesion of the disease was removed, in the population most likely to benefit, and roughly two-thirds to three-quarters of the clinical trajectory proceeded regardless.

That is precisely what Boyle's attributable-risk arithmetic predicts. If 41 per cent of Alzheimer's dementia is attributable to pathologic Alzheimer's disease, and if the antibody addresses only the amyloid half of that pathology, and if it is given after the process is symptomatic, then a residual of two-thirds is not a disappointment. It is the number.

The trials therefore refute the nosology and confirm the pathology in the same eighteen months. Amyloid is causal — Kalvach is wrong about that, or at least wrong to treat it as merely accompanying. Amyloid is also a minority contributor to the syndrome that bears its name — Kalvach is right about that, and the trials are the best evidence for it yet obtained, because they are the only evidence in which the amyloid contribution has been experimentally subtracted rather than statistically estimated.

We note one further asymmetry the essay would have enjoyed. Both trials required biomarker-confirmed amyloid positivity for entry. The 32 per cent of clinically diagnosed patients who are amyloid-negative — a figure the essay cites — were not eligible for either drug. The therapeutic era has begun by excluding from treatment a third of the people who carry the diagnosis, on the grounds that they do not have the disease as biologically defined. Whatever that third has, it is producing the clinical picture of Alzheimer's disease without the biology of Alzheimer's disease, and no one is developing a drug for it.

Grade: Contradicts the claim that amyloid is merely accompanying (human, randomised, replicated). Supports the claim that Alzheimer pathology is a minority contributor to the syndrome (human, randomised, replicated).

20. The Field Went the Other Way

Kalvach's final substantive paragraph objects to the biological definition of Alzheimer's disease in asymptomatic people. He accepts the 2018 NIA-AA framework's statement that the term refers to an aggregate of neuropathologic changes and that dementia is a syndrome caused by multiple diseases; he rejects the promotion of lifelong histological change to disease status in the absence of clinical manifestation.

Four years later the field committed to the position he rejected, in stronger terms.

The 2024 revised criteria of the Alzheimer's Association Workgroup state the commitment in their own highlights: *"We define Alzheimer's disease (AD) to be a biological process that begins with the appearance of AD neuropathologic change (ADNPC) while people are asymptomatic. Progression of the neuropathologic burden leads to the later appearance and progression of clinical symptoms."* The document's stated rationale is that defining diseases biologically rather than syndromically has long been standard in other areas of medicine, and is becoming a unifying concept across neurodegenerative disease (Jack et al., 2024).

Two observations follow, and they are not the ones usually made.

The first is that the 2024 criteria make Kalvach's objection sharper, not weaker. Under a biological definition anchored to core biomarkers, a person with a positive amyloid PET or an abnormal plasma phospho-tau 217 has Alzheimer's disease. Braak's series puts abnormal tau in 99.6 per cent of brains and amyloid plaques in 75 per cent of people in the tenth decade. Amyloid positivity among the cognitively intact runs at 14–47 per cent. The biological definition therefore assigns the diagnosis to a very large fraction of the healthy elderly — and Kalvach's question, which was rhetorical in 2020, becomes operational in 2026: what is the clinical meaning of a disease that a quarter to a half of well people have?

The second is that the analogy to oncology, which is the criteria's own justification, is doing more work than it can bear. In oncology, defining the disease biologically works because the biological entity is discontinuous with the surrounding tissue, because it is not present in the majority of the healthy, and because detecting it early leads to an intervention that changes outcomes. The first two conditions do not hold for Alzheimer neuropathologic change. The third is now partly satisfied for amyloid-positive symptomatic people and remains unsatisfied for the asymptomatic. That is not an argument against biological definition; it is an argument that the analogy imports a promise the biology does not currently keep.

We record, for balance, the strongest case for the 2024 position, which the essay never engages. Syndromic definitions of this disease have performed badly. They produced a clinicopathological match rate that the essay itself cites at 64 per cent, with 37 per cent of clinically diagnosed Alzheimer cases failing to match pathologically. A definition that is wrong a third of the time is a poor foundation for a therapeutic era in which the treatments are lesion-specific and carry a real risk of amyloid-related imaging abnormalities — 12.6 per cent with oedema or effusion on lecanemab, 24.0 per cent on donanemab. If you are going to give a drug with that risk profile, you had better know the lesion is there. Biological definition earns its keep as an *inclusion criterion for treatment*, whatever its merits as a nosology.

Which suggests the resolution neither side has reached: the biological definition is a good tool for deciding whom to treat and a bad tool for telling someone what they have.

Grade: The essay's objection is Supported and strengthened by subsequent events; its implied remedy — abandoning biological definition — is Contradicted by the therapeutic requirements of the 2023–2026 era.

21. Two Entities Built to Solve His Problem

Between 2014 and 2019 the field created two new diagnostic categories, and both exist because of the problem Kalvach is describing.

Primary age-related tauopathy was proposed in 2014 for brains with neurofibrillary change in the medial temporal and brainstem distribution, in the effective absence of amyloid — a pattern the consensus paper describes as a common pathology associated with human ageing (Crary et al., 2014). Its purpose is to give a name to the tau that everybody has.

Limbic-predominant age-related TDP-43 encephalopathy was proposed in 2019 for a TDP-43 proteinopathy with a hippocampal-sclerosis association that mimics Alzheimer's disease clinically and is highly prevalent in the very old (Nelson et al., 2019). Its purpose is to give a name to a large slice of what was previously being called Alzheimer's disease.

Both are useful. Both are also, structurally, subtractions from the disease category, and it is worth being explicit about what they subtract.

PART removes from Alzheimer's disease the pathology that is nearly universal and mostly non-dementing. LATE removes from Alzheimer's disease a large fraction of the late-life dementia that Alzheimer pathology was previously being credited with — LATE neuropathologic change is present in about a third of oldest-old brains, and in The 90+ Study 31 per cent of participants had it. What remains after both subtractions is a smaller, more specific entity with a better claim to being a disease.

Kalvach would read this as vindication, and in one sense he should. Two committees independently concluded that the category as it stood contained things that did not belong in it, which is his thesis restated in the field's own procedural language.

But the correct reading is more interesting than vindication, and it runs against him. **The subtraction procedure works.** A category that can be improved by removing well-characterised, separately-named entities from it is not an incoherent category; it is a category undergoing normal scientific refinement. The presence of PART and LATE is evidence that the disease concept is *revisable*, which is the opposite of the essay's implication that it is a construct maintained by momentum.

And there is a cost the essay would want counted. In The 90+ Study, LATE neuropathologic change occurring *without* Alzheimer neuropathologic change and without Lewy bodies was found in only 5 of 364 autopsies — 1.4 per cent — and all five still had tau. The pure forms are vanishingly rare. Splitting a mixed phenomenon into named pure entities produces categories that almost nobody instantiates, which is a real problem for a nosology and the strongest form of Kalvach's complaint. The brains do not come apart along the lines the committees draw.

Grade: Mixed. The categories vindicate the diagnosis of the problem and refute the prognosis.

22. What the Category Buys, and What It Costs

We can now state the nosological question as a decision problem, which is the form in which it can actually be answered, and which the essay never puts it in.

Calling a cluster of findings a disease is not a discovery about nature. It is a decision with consequences, and the consequences are enumerable.

What the category buys.

Regulatory tractability. Drugs are approved for diseases. There is no regulatory pathway for "the far tail of brain ageing," and no sponsor will run a 1,795-person eighteen-month trial without one. Lecanemab and donanemab exist because Alzheimer's disease exists as a category.

Research funding at scale. The same argument, applied to public money.

Clinical communication. A patient asking what is wrong is asking for a name, and "you are ageing unusually fast in the medial temporal lobe" is a worse answer than the one they get, even if it is more accurate.

Cohort definition. Nothing in §§6–11 could have been discovered without a category to define the cases against.

What the category costs.

Misallocation. If 41 per cent of the syndrome is attributable to the eponymous pathology and near-100 per cent of the therapeutic effort has been aimed at it, the category has directed resource in proportion to its name rather than its share.

The excluded third. The 32 per cent of clinically diagnosed patients who are biomarker-negative are, under the biological definition, category errors. They have the syndrome and not the disease, and there is no research programme aimed at them because there is no name for what they have.

False promise. A disease implies a cure. A near-universal, multi-causal, decades-long degenerative process implies risk reduction and delay. The gap between those two implications is where public disappointment with this field has come from, and the essay's irritation at the war metaphor is an irritation at that gap.

Fear. The essay's most human argument, and its weakest-evidenced: that calling this a relentless killer and a worldwide epidemic serves "only to an improper fear induction." Kalvach cites discourse analysis rather than data on outcomes, so this cannot be graded. It can be noted that a condition affecting under half of the population at ninety is not well described as an epidemic, and that the descriptive inaccuracy is on the side of the alarm.

The honest conclusion is not the essay's. It is that the category is a **tool with a favourable balance for treatment and an unfavourable balance for understanding**, and that the correct response is to keep it for the first purpose while refusing to let it organise the second. That is a smaller conclusion than "it is not a disease." It is also one the evidence supports.

Part V — The Corollary He Declines

23. Reachability Zero

Read the essay to the end and something is missing that no summary of its content will show you: it never says what to do.

There is no proposed intervention. No target, no trial design, no screening strategy, no clinical recommendation. The closest it comes is a single conciliatory sentence — "all attempts for understanding the degenerative processes and deferring their impact are of utmost importance" — which names no attempt and defers to nothing in particular.

This is not a small omission and it is not an accident of length. Thirteen pages is enough to propose something. It is a structural feature of the argument as constructed, and it has a specific cause: **the essay's entire rhetorical energy is spent on demolition, and demolition of a category leaves nothing standing to act on.** If Alzheimer's disease is not a thing, the reader's next question is what should be done instead, and the essay treats the question as beyond its scope.

We think this is the single largest missed opportunity in the document, larger than any of the errors catalogued in Part III, and for a reason that is worth stating carefully. **The argument has a therapeutic corollary. It is obvious. It is not drawn.**

The corollary is this. If dementia is the far tail of brain ageing, then the modifiable variable is the *rate of brain ageing*, and the target is not a lesion but a process. That is a real research programme with a name, a literature, live clinical trials and an available first patient. The essay is one sentence from it and never writes the sentence.

The remainder of this Part writes it, in three parts: the geroscience the thesis implies, the vascular target the author's own career implies, and the one narrow structural claim in the essay that is already actionable and that nobody has followed up.

24. If It Is Ageing, Treat Ageing

The geroscience hypothesis holds that the biological processes of ageing are the common upstream driver of the major age-related diseases, and that intervening on those processes should shift the whole family of outcomes rather than one at a time. It is the exact positive counterpart of Kalvach's negative thesis: he says the disease is ageing; geroscience says therefore treat ageing.

Three lines of evidence connect his argument to that programme, and one of them is already in his bibliography.

The epigenetic clock, which he cites and does not follow. Reference 196 of the essay is Degerman and colleagues, who measured DNA-methylation age in blood at baseline (age 55–65) and fifteen years later in 52 age- and sex-matched participants from the Betula study stratified by memory trajectory. Those with maintained memory had a lower delta DNAm age than those with average decline ($p = 0.035$) or accelerated decline ($p = 0.037$). And — the finding the essay does not mention — **methylation age at follow-up predicted dementia ($p = 0.019$) while chronological age did not** (Degerman et al., 2017).

Consider what that result does inside Kalvach's own framework. His thesis is that dementia is a function of ageing. Here is a study in which a *biological* measure of ageing predicts dementia and the *chronological* measure does not. That is his thesis confirmed and sharpened in one step: it is not the years that matter but the rate, and the rate is measurable in a blood sample. He cites the paper for the modest observation that memory maintainers have a younger epigenetic age, and stops.

If the rate is measurable, it is an endpoint. If it is an endpoint, it can be moved. That is the argument he needed and had.

Senolytics, the first geroscience intervention to reach an Alzheimer's population. Cellular senescence is one of the canonical hallmarks of ageing, and senescent cells accumulate in aged brain. An open-label phase I trial of intermittent oral dasatinib and quercetin in five participants with early symptomatic Alzheimer's disease established central nervous system penetrance of dasatinib — detected in cerebrospinal fluid in four of five participants, at CSF-to-plasma ratios of 0.4–0.9 per cent — with acceptable tolerability and no early discontinuations. Cognitive and neuroimaging endpoints did not differ from baseline, which in a five-person twelve-week feasibility study is the expected result and is reported as supporting safety rather than efficacy (Gonzales et al., 2023).

This is a very small study and we will not oversell it. What it establishes is a single thing that matters for the present argument: **the ageing-process target is now reachable in this patient population.** A drug aimed at a hallmark of ageing rather than at a lesion of Alzheimer's disease crossed into the central nervous system of people with Alzheimer's disease. Whatever the essay's thesis implies therapeutically, it is no longer implying it about an inaccessible target.

The prevention trials, which are geroscience by another name. FINGER, SPRINT MIND and US POINTER do not describe themselves as ageing interventions. But what they manipulate — vascular risk, physical activity, diet, cognitive and social engagement — is not lesion-directed. None of them targets amyloid, tau, TDP-43 or α-synuclein. They target the substrate on which those lesions land, which is to say they target the rate at which the brain ages. On Kalvach's own account these are the correctly-aimed trials in the field, and he does not mention them.

The honest statement of where this stands. Geroscience in dementia has a strong rationale, one first-in-human safety signal, and no efficacy evidence. It is at the stage the amyloid programme was at around 1995. Anyone who tells you it is more than that is selling something, and the position statement Kalvach cites as reference 1 was written by fifty-two researchers specifically to say so. But "no efficacy evidence yet" is a different sentence from "nothing to do," and the essay's silence reads as the second when the first is what its argument warrants.

25. The Organ He Actually Knows

There is a second corollary, closer to home, and the essay's failure to draw it is stranger than the first because the author spent his career on it.

The essay's own evidence identifies an axis: processing speed declines earliest and most linearly; white-matter disease damages processing speed specifically; white-matter disease begins in the fifth decade and progresses in nearly everyone; and the neuropsychological, imaging and neuropathological literatures converge on it independently. That axis is not the medial temporal lobe. It is the connective tissue of the brain, and it is the tissue whose principal determinant is vascular.

It is also, unlike almost everything else in this disease, **treatable at population scale by existing means.**

White-matter hyperintensity burden is driven substantially by blood pressure. Hypertension is one of the fourteen factors in the 2024 Lancet Commission's 45 per cent. SPRINT MIND, whatever its miss on the primary dementia endpoint, showed that intensive systolic control reduced mild cognitive impairment and the composite of MCI or probable dementia in hypertensive adults — and the trial's cognitive outcomes were limited in part because the parent trial was stopped early for mortality benefit, which is to say the intervention worked too well on a different endpoint to be evaluated properly on this one.

Set that beside the essay's structure. Kalvach's white-matter case is the best-evidenced part of the document, drawn from the field he practised in, and it points directly at the single most modifiable risk factor in the Lancet Commission's list. He assembles the case and does not close it. The sentence he needed is: *if the earliest and most consequential change in the ageing brain is white-matter rarefaction driven by small-vessel disease, then blood pressure is the most valuable target in dementia and it is available now.*

We should say what we think happened, since it bears on how to read documents of this kind. The essay is organised as a refutation of a nosology, and a refutation has no place to put a positive recommendation. Having decided to argue that Alzheimer's disease is not a disease, the author had no structural slot for the claim that a component of it is eminently treatable, because that claim sounds like a concession. It is not a concession. It is the strongest thing his evidence supports.

26. The Fornix: One Narrow Gate, Unfollowed

The essay contains exactly one original structural argument, it is three sentences long, and it is the most actionable thing in the document.

"Fornix plays a key functional role in connecting memory deposits with limbic association centres of integrated awareness and with frontal supervisory centres. If having only about one million axons even minimal lesions in these fasciculi are capable of causing much bigger functional deficits than major lesions elsewhere in the hemispheres."

The argument is a bottleneck argument. Most white-matter damage in the ageing brain is diffuse and its functional cost is roughly proportional to its extent, because the tissue it destroys is redundant. But a tract that carries the entire hippocampal output through a small, spatially confined bundle has no redundancy: damage there is not proportional to volume but to position. A one-per-cent lesion in a bottleneck can cost more than a ten-per-cent lesion in a field.

The supporting evidence he cites is real. Fornix fractional anisotropy is associated with working memory, episodic memory and verbal and visual recall; loss of fornix white-matter volume predicts cognitive impairment in cognitively normal elderly individuals (Fletcher et al., 2013); fornix integrity together with hippocampal volume predicts memory decline and progression to Alzheimer's disease; and fornix microstructure interacts synergistically with β-amyloid to accelerate decline in clinically normal older adults. His own summary — that fornix microstructure "had the greatest impact on both functional connectivity and memory performance" — is a strong claim, and it is the kind of claim that a bottleneck architecture predicts and a diffuse-damage model does not.

He also cites, as reference 185, a review of the anatomy and function of the fornix explicitly framed around its potential as a therapeutic target (Senova et al., 2020) — and does not say what the therapy is.

It is deep brain stimulation, and it has been tried. A phase II randomised double-blind trial of bilateral fornix DBS in 42 patients with mild Alzheimer's disease found the procedure safe and well tolerated, with increased cerebral glucose metabolism at six months, and **no significant difference on either primary cognitive outcome at twelve months** for the cohort as a whole. On post-hoc analysis there was an age interaction: patients aged 65 and over trended toward benefit, while the twelve patients under 65 trended toward being worse with stimulation on (Lozano et al., 2016).

That is a negative trial with a hypothesis-generating subgroup, and it should be treated as such. But note the direction of the interaction, because it is the one Kalvach's thesis predicts and nobody has read it that way. **The intervention aimed at the bottleneck helped the older patients and possibly harmed the younger ones.** If the younger patients in a mild-Alzheimer's trial are enriched for the aggressive, amyloid-driven, genetically-loaded form of the disease, and the older ones for the diffuse multi-pathology form, then a circuit-level intervention that compensates for distributed connectivity loss would be expected to do exactly this: help where the problem is throughput and fail where the problem is a lesion.

We do not claim this is established. We claim it is an available and untested reading of an existing dataset, generated by taking Kalvach's framework seriously, and that it is the sort of thing his argument is good for. A nosological claim that cannot generate a prediction is idle; this one generates one.

The experiment it implies is in Part VII, ranked third.

Part VI — What Survives

27. The Reformulation

An evaluation that only subtracts is a poor return on the reading. What follows is the strongest thesis the evidence in Parts II and III jointly supports. It is not Kalvach's thesis. It keeps everything his evidence establishes, discards the one step it cannot support, and — this is the point — is more useful than either the position it replaces or the position it was arguing against.

Alzheimer's disease is not a disease *of* ageing. It is a disease *within* ageing, whose entry is near-universal and whose exit is determined by something else.

Four propositions, in order.

One — entry is not the interesting variable, because almost everyone enters. Abnormal tau is present in about 99.6 per cent of human brains. Amyloid plaques reach 75 per cent by the tenth decade. Primary age-related tauopathy is found in 45 per cent of a forensic series aged 40 and over. Whatever initiates this process initiates it in nearly everybody. A risk factor that everyone has explains nothing about who becomes demented, and the field's decades-long focus on initiation has been a focus on the one part of the system with no variance in it.

Two — exit is the interesting variable, and it is not determined by traversal. A substantial fraction of people complete the pathological arc and do not become demented. In the MRC CFAS series, the odds ratio linking neocortical neuritic plaques to dementia fell from 8.63 at 75 to 2.48 at 95, its confidence interval crossing unity. In The 90+ Study, participants with intermediate or high Alzheimer pathology alone were 3.5 times more likely to be demented, while those with a single non-Alzheimer pathology were 12.4 times more likely. Pathology and outcome are loosely coupled, and the coupling loosens with age.

Three — the variable that decides the exit is resilience, and resilience is partly environmental. This is the claim the reformulation adds and Kalvach's version cannot accommodate, because his version requires the outcome to be fixed. It is not fixed. Age-specific incidence fell 44 per cent across three Framingham epochs, 13 per cent per decade across seven cohorts and 49,202 people, and about 20 per cent across two decades in a study designed to hold method constant — all in the absence of any treatment for the pathology. Prevalence in the United States fell from 11.6 to 8.8 per cent between 2000 and 2012 *while cardiovascular risk in the same population worsened*, with rising education accounting for part of the change. The pathology, so far as anyone knows, did not change. What changed was the brain's capacity to carry it.

Four — therefore the target is resilience, and it is the only part of this system currently known to be modifiable at population scale. The 45 per cent attributable fraction, the multidomain trials, the blood-pressure evidence, the education effect: every one of these acts on the brain's capacity to tolerate pathology rather than on the pathology itself. That is not a second-best target. On the evidence above it is the target with the demonstrated population effect, and the lesion-directed programme is the one with a demonstrated 27–35 per cent effect in a pre-selected minority.

What this reformulation costs Kalvach. It abandons "not a disease." Alzheimer's disease on this reading is a real, causally-identified pathological process, demonstrated by the antibody trials and by the autosomal-dominant and trisomy-21 cases, that contributes about two-fifths of the syndrome named after it.

What it costs the field. It abandons the premise that understanding initiation is the route to prevention. If everyone initiates, the initiation mechanism is not where the answer is.

What it keeps of the essay. Everything that made it worth evaluating: the universality, the continuity, the marker failure, the mixed pathology, the white-matter axis, the attenuation with age, and the insistence that the category is doing work it has not earned.

28. The Ledger

Twenty-two claims, graded. **Direction** is stated relative to Kalvach's essay: *Established* (the essay's claim is right and the evidence is decisive), *Supported*, *Mixed*, *Contradicted*, or *Unresolved*. **Maturity** runs M1 (human, population-scale or replicated across independent cohorts) to M5 (in vitro, model organism, or inference from adjacent findings).

#	Claim under test	Direction	Mat.	Principal evidence
1	Alzheimer-type pathology is present in effectively all aged humans	Established	M1	Braak 2011, n=2,332; 10 AT8-immunonegative
2	Abnormal tau appears first in the locus coeruleus in a subset with no cortical involvement	Established	M1	Braak 2011, 58 subcortical-only cases
3	Age-related cognitive decline begins in the third decade in healthy adults	Established	M1	Salthouse 2009; Schaie Seattle Longitudinal
4	Processing speed is the earliest and most linear domain of decline	Established	M1	Schaie 1994; Salthouse; Kail
5	No boundary between normal and morbid senescence has been found in any measured domain	Established	M1	Convergent across §7 literatures
6	Amyloid burden does not track cognition in the non-demented	Established	M1	Hedden meta-analysis, 64 studies, n=7,140
7	~32% of clinically diagnosed Alzheimer patients are amyloid-negative	Established	M1	Doraiswamy 2012 and successors
8	Dementia in the community is predominantly mixed pathology	Established	M1	Boyle 2019; Schneider 2007; Kawas 2015
9	Pathologic AD accounts for ~41% of Alzheimer's dementia	Established	M1	Boyle 2019, n=1,161
10	In the oldest old a single non-AD pathology carries higher dementia odds than AD alone	Established	M1	Kawas 2015, n=183 (OR 12.4 vs 3.5)

#	Claim under test	Direction	Mat.	Principal evidence
11	The pathology–dementia association attenuates with age; the atrophy–dementia association does not	Established	M1	Savva 2009, n=456 — **cited but unused by the essay**
12	White-matter lesions are near-universal in the elderly and track processing speed	Established	M1	Debette & Markus meta-analysis; Xiong & Mok
13	Blood–brain barrier breakdown is an early biomarker independent of Aβ and tau	Supported	M2	Nation 2019
14	Clinical retrogenesis: losses recapitulate acquisitions in reverse	Established	M2	Reisberg 1999, FAST
15	Pathogenic retrogenesis: last-myelinating regions degenerate first	Contradicted	M2	Two-rule conflation; no allocortex rank; LC born E9
16	Defective cerebrovascular reactivity underlies early leukoaraiosis	Contradicted	M2	**Peisker & Kalvach 2010 — r = 0.01, 0.08; the essay's own source disclaims it**
17	Dementia prevalence exceeds 50% by age 85–90	Contradicted	M1	Corrada 2008: 45% women, 28% men at 90+
18	Dementia incidence is near-certain at extreme age	Supported	M1	Corrada 2010: 40.7%/yr at 100+
19	Dementia is an inevitable toll of long life	Contradicted	M1	Satizabal 2016 (−44%); Wolters 2020 (−13%/decade, n=49,202); Matthews 2016 (−20%); Langa 2017
20	A substantial fraction of dementia is attributable to modifiable factors	Contradicted (vs essay)	M2	Livingston 2024 (~45%, 14 factors); FINGER; POINTER
21	Alzheimer's disease requires an aged brain	Contradicted	M1	Bateman 2012 (DIAN); Fortea 2020 (DS, prodromal at 50.2 y)
22	Amyloid is an accompanying feature rather than a cause	Contradicted	M1	van Dyck 2023; Sims 2023 — randomised, replicated

Summary of the ledger. Twelve claims Established, two Supported, eight Contradicted. Every Established claim is descriptive; every Contradicted claim is inferential. That is the shape of the essay in one sentence: **the observations are right and the conclusions drawn from them are not.**

Two entries carry a mark because they are findings of this evaluation rather than of the literature: claim 11, the strongest evidence in the essay's bibliography for the essay's own thesis, cited for something else; and claim 16, a citation used against the stated conclusion of its own source, that source being the author's own laboratory.

29. Five Conditions of Refutation

The reformulation of §27 is only worth having if it can fail. These five results would break it, and each is obtainable.

R1 — Entry stops being near-universal. If a modern, adequately-powered autopsy or biomarker series with full-brain sampling finds that a substantial minority of the aged — say a third or more — are genuinely free of Alzheimer-type change, then entry has variance after all, and the claim that initiation cannot discriminate fails. *Currently:* the Braak series says otherwise at n = 2,332, but it is a single centre with a single staining protocol, and no equivalently large independent series exists.

R2 — The secular decline turns out to be pathology, not resilience. If brains from people born in 1940 carry *less* Alzheimer neuropathologic change at a given age than brains from people born in 1910, then falling incidence reflects less disease rather than better tolerance of it, and the resilience claim in §27 collapses into a prevention claim. *Currently:* untested. This is the first experiment in Part VII.

R3 — A discrete boundary is found. If any variable — biomarker, imaging, transcriptomic, electrophysiological — is shown to have a bimodal or step distribution separating demented from non-demented individuals, independent of the diagnostic criteria used to define them, the continuity claim fails. *Currently:* fifty years of searching has produced gradients in every domain.

R4 — Resilience turns out to be fixed. If the falling incidence is fully explained by cohort composition, survivorship or diagnostic drift, and correctly-designed studies holding these constant find no change, then resilience is not modifiable and Kalvach's inevitability claim is rehabilitated. *Currently:* CFAS II was built to test exactly this and found a fall.

R5 — Lesion removal proves sufficient. If an anti-amyloid or anti-tau agent given early enough produces something approaching arrest rather than 27–35 per cent slowing, the mixed-pathology account is wrong and the eponymous lesion was the disease after all. *Currently:* the primary-prevention trials in autosomal-dominant and biomarker-positive asymptomatic populations are the ones that will answer this, and they are running.

Note the asymmetry, which is the honest thing to record about this reformulation. **R2 and R5 are the two that could kill it, and both are experiments in progress or available.** R1, R3 and R4 test propositions with fifty years of consistent evidence behind them and are unlikely to

move. A framework whose live falsifiers are the ones nobody has run yet is in a better position than one whose falsifiers have all been attempted, but it is not yet a framework that has survived anything.

Part VII — Ten Experiments, in Order

The order is by information yield per unit of difficulty, not by ambition. Each is stated as a question with a decision rule, because an experiment whose result would not change anybody's next move is not worth ranking.

3o. The Ten

1. The secular trend in *pathology*, not in dementia.

Question. Do brains from later-born cohorts carry less Alzheimer neuropathologic change at a given age than brains from earlier-born cohorts?

Design. Birth-cohort-stratified re-analysis of existing large autopsy archives — CFAS, Religious Orders Study and Rush Memory and Aging Project, the Nun Study, the Vantaa 85+ cohort — holding staining protocol and staging criteria constant, with age at death and sex matched across cohorts. The tissue already exists. The protocols already exist. This is a database and a pathologist, not a new study.

Decision rule. If the pathology burden is unchanged while incidence has fallen by a quarter, the falling incidence is **resilience**, and every prevention programme aimed at reducing pathology is aimed at the wrong endpoint. If the pathology burden has fallen, the decline is genuine **prevention**, and the resilience framing of §27 is wrong.

Why it is first. It is the cheapest experiment on this list and it discriminates between the two dominant interpretations of the most important epidemiological fact in the field. Nobody has run it.

2. Resilience as the primary endpoint.

Question. Can an intervention be shown to increase the amount of pathology a person tolerates without becoming demented?

Design. Any prevention trial with biomarker-confirmed pathology at baseline, powered on the *interaction* between pathology burden and cognitive trajectory rather than on cognition alone. The multidomain trials already collect what is needed; the analysis is different, not the data.

Decision rule. A demonstrated increase in tolerated burden would establish resilience as a manipulable quantity, which no trial has yet done. Absence of interaction would mean the multidomain effect operates through the pathology after all.

3. Re-analysis of fornix deep brain stimulation stratified by pathology profile.

Question. Does the age interaction in the phase II fornix DBS trial reflect a difference in the *kind* of disease rather than a difference in age?

Design. Retrieve the 42-patient dataset. Stratify not by age but by available markers of the amyloid-driven versus multi-pathology phenotype — amyloid burden, *APOE* genotype, white-matter hyperintensity volume, vascular risk score. Test whether benefit tracks the multi-pathology phenotype rather than the birthday.

Decision rule. If circuit-level stimulation helps the diffuse-pathology patients and harms the lesion-driven ones, the bottleneck reading of §26 is supported and the design of the successor trial should be changed. If the interaction is genuinely with age and not with phenotype, the reading fails.

Why it is third. The data exist, the analysis is a week's work, and a successor trial is being designed on the assumption that age is the moderator.

4. Whether the excluded third has a disease.

Question. What is wrong with the ~32 per cent of people carrying a clinical Alzheimer's diagnosis who are biomarker-negative?

Design. Prospective deep phenotyping of biomarker-negative clinically-diagnosed patients — full neuropathological panel at autopsy, plasma p-tau217 and neurofilament light trajectories, white-matter and small-vessel quantification, TDP-43 proxies, systematic screening for the non-degenerative mimics. Follow to death.

Decision rule. If this group resolves into LATE, vascular disease and hippocampal sclerosis in known proportions, the biological definition is doing its job and the group is misdiagnosed. If a substantial fraction has no identifiable pathology, that is Boyle's unattributable third made visible in living people, and it is the largest unexplored population in the field.

5. Ordering the two clocks.

Question. Which comes first in the same individual — the white-matter/processing-speed decline or the medial-temporal/episodic-memory decline — and does the order predict the eventual syndrome?

Design. Existing longitudinal cohorts with both diffusion imaging and domain-resolved psychometrics from midlife. Model individual-level onset times for each axis. Ask whether people whose speed axis fails first arrive at a different clinical endpoint from those whose memory axis fails first.

Decision rule. If the two axes have independent onset times and predict different endpoints, they are two processes and the disease category is combining them. If they are locked, they are one process and the category is right to combine them.

6. Epigenetic age as an intervention endpoint in dementia prevention.

Question. Does an intervention that slows methylation-age acceleration also slow cognitive decline?

Design. Add serial methylation-age measurement to running multidomain prevention trials. The blood is already banked in several.

Decision rule. Concordant movement of methylation age and cognition would make rate-of-ageing a surrogate endpoint for dementia prevention, which would shorten every trial in the field. Discordance would show that the two are independent, which is equally informative and would retire a popular assumption.

7. Primary-age-related tauopathy: entity or stage?

Question. Is PART a distinct condition, or is it Alzheimer's disease in people who died before the amyloid arrived?

Design. Longitudinal biomarker follow-up of living people meeting PART criteria on tau PET with negative amyloid PET, to determine what fraction convert to amyloid positivity and over what interval, against age- and *APOE*-matched controls.

Decision rule. High conversion means PART is a stage and the category is bookkeeping. Low conversion means it is an entity, and the near-universal tau of §6 is genuinely not the same thing as Alzheimer's disease — which would be the strongest possible vindication of Kalvach's core intuition and the clearest refutation of his conclusion, since it would mean the disease is rarer and more specific than he thinks.

8. Blood pressure trials powered on dementia.

Question. What is the true effect of long-term blood-pressure control on dementia incidence, in a trial not stopped early for mortality?

Design. Pooled individual-participant analysis of existing antihypertensive trials with cognitive follow-up, extended by long-term observational follow-on of randomised arms.

Decision rule. A confirmed effect on dementia would make hypertension the largest reachable target in the field and would reorient prevention away from lesion-directed strategies. This experiment is unglamorous and is probably worth more than most of the ones above it.

9. Whether the pathology–dementia attenuation with age replicates.

Question. Does the Savva result — plaque odds ratio falling from 8.63 at 75 to 2.48 at 95 while atrophy holds — replicate in independent series with modern panels?

Design. Age-interaction models in the large community autopsy cohorts, scoring the full modern panel including TDP-43, hippocampal sclerosis and arteriolosclerosis, and testing whether the attenuation survives adjustment for co-pathology or is produced by it.

Decision rule. If the attenuation is a co-pathology artifact — Alzheimer pathology appearing to matter less at 95 because so much else is present — it is a different and less interesting finding. If it survives adjustment, the disease genuinely becomes less explanatory with age, and claim 11 of the ledger is one of the most important results in the field.

10. The category, tested as an instrument.

Question. Does diagnostic labelling change outcomes?

Design. This is not a trial anyone will run, so state it as an audit: compare care pathways, treatment allocation, prognostic accuracy and patient-reported outcomes between people diagnosed under syndromic criteria and people diagnosed under biological criteria, in health systems that adopted the 2024 framework at different times.

Decision rule. Kalvach's nosological claim is ultimately a claim that the category harms. It has never been measured. The natural experiment of staggered adoption makes it measurable, and a nosological argument that declines to be measured is philosophy rather than medicine.

A closing note on the order. Experiment 1 is first because the single most consequential fact in this literature — that age-specific dementia incidence has been falling for thirty years — has two available explanations with opposite therapeutic implications, and the tissue that would distinguish them is sitting in freezers. Kalvach's essay is wrong that the process is inevitable. Nobody yet knows why it is not, and the answer determines what the field should do next.

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A note on verification. Every reference in the first list was retrieved from PubMed and checked against the indexed record — author list, journal, year, volume, pages — and, wherever a figure or a quotation appears in the text above, against the source's own abstract or full text. References in the second list are given *as they appear in Kalvach's bibliography*, because it is his use of them that is under discussion; they were not independently re-verified for this evaluation, and no quantitative claim made in this paper rests on one of them alone.

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