The Scheduled Withdrawal

Anne Eckert's neuroendocrine and bioenergetic theory of Alzheimer's disease in women: the two arrows her laboratory closed, the only clock in the disease that can be read in advance, and the compensation whose failure is the illness

Complex I and complex IV · The dated exposure · The second fuel · The failed switch · The trials that measured the wrong thing · The male half

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Every woman who lives past midlife undergoes the same endocrine event on roughly the same schedule, and her brain loses roughly the same fraction of its glucose supply. Most women never become demented. This paper argues that the interesting quantity is therefore not the withdrawal but the adaptation to it — a switch to a second fuel that is measurable, dated, and sometimes fails.

Contents

Abstract

In 2020 a pharmacologist at the University of Basel submitted a ten-page paper proposing that Alzheimer's disease in women begins at the menopause. The mechanism she named was not a protein. It was a fuel supply. The withdrawal of oestradiol removes a hormone that regulates glucose transport, glycolysis, the Krebs cycle, oxidative phosphorylation and the antioxidant enzymes that keep the resulting radicals in check; the brain that loses it must either find another way to pay for itself or fail. Her title called the transition *an entry door*.

This paper evaluates that proposal. It grades the mechanism against the laboratory record, the timing claim against the human record, and the therapeutic programme against six years of trial evidence that postdates the manuscript. It concludes that the theory is substantially right about the organelle, only half-supported on the epidemiology it leads with, and most valuable in a claim its author states in a single paragraph and never presses.

The mechanistic work is unusually well-anchored, and one result in it is a genuine dissociation. Across a fifteen-year programme in Frankfurt and Basel, Eckert's laboratory and its collaborators established that the two proteins of Alzheimer's disease damage the respiratory chain at different places. In triple-transgenic mice carrying both pathologies, quantitative proteomics across 1,275 proteins found deregulation of complex I to be *tau*-dependent and deregulation of complex IV to be *amyloid*-dependent, at both the protein and the activity level, with a synergistic collapse of mitochondrial membrane potential at eight months that neither single-transgenic strain showed. That is not a claim that mitochondria are involved. It is a claim about which lesion sits where, and it is falsifiable.

The same laboratory closed the loop in the other direction. Most accounts of a mitochondrial "vicious cycle" assert both arrows and demonstrate one. Crossing a mitochondrially compromised mouse — the Harlequin mutant, which lacks apoptosis-inducing factor — into a P301L tau line produced *more* tau pathology and more apoptotic neurodegeneration than either mutation alone. Tau damages mitochondria; damaged mitochondria make more tau pathology. Both arrows are now animal facts, and they were established by the same group.

A third result from that programme has been almost entirely overlooked, including by its authors. In the cell model, overexpressing *wild-type* tau did not merely fail to harm the respiratory chain — it *raised* complex I activity and improved mitochondrial dynamics, while the P301L mutant lowered both. If normal tau is a positive regulator of complex I, then the tauopathies include a loss of a housekeeping function and not only the gain of a toxic one, and a therapeutic strategy of lowering total tau is removing something the mitochondrion was using. We treat this as one of the more consequential unexploited findings in the body of work under review.

The clock is the real contribution, and it is a contribution of a kind the field has almost none of. Every biomarker in Alzheimer's disease dates the process retrospectively: you learn when a person's amyloid began accumulating by scanning them after it has. Menopause dates itself, prospectively, in half the population, at a median age near 51, without instrumentation, roughly two decades before the median age of symptomatic disease. Whatever else is true of this theory, it identifies the only exposure in late-onset Alzheimer's disease that can be diarised in advance. The paper's most translatable page is its last figure, which stages women by menstrual status and assigns each stage a different investigation and a different intervention.

But the epidemiological premise the paper opens with does not support the theory, and three of its own citations say so. The submission leads with the observation that women are two-thirds of Alzheimer's patients and dismisses longer female survival as "rather simplistic." The review it cites for the two-thirds figure gives competing mortality as its leading explanation and notes that men may carry the higher risk of mild cognitive impairment. The twin-registry study it cites for a post-80 incidence difference states in its own abstract that the pattern "is consistent with women's survival to older ages." In Framingham, followed from mid-adult life, cumulative incidence of dementia was *similar* in women and men; the excess appears in lifetime risk, which is a survival-weighted quantity. The correct statement is that the sex difference in prevalence is largely demographic and the sex difference in *biology* is real but must be argued from biomarkers rather than from a headcount. Eckert has the biomarker evidence and leads with the headcount.

The biomarker case, which she uses second, is much stronger than the one she uses first. In 121 cognitively normal adults aged 40 to 65, women showed higher amyloid deposition, lower glucose metabolism and lower grey and white matter volumes than men, and after female sex itself, *menopausal status* was the risk factor most consistently associated with those differences. In a multimodality study of the transition, abnormality was graded — greatest in post-menopausal, intermediate in peri-menopausal, least in pre-menopausal women — and absent in age-matched men. Among cognitively unimpaired adults, entorhinal tau was higher in women than in men at a given amyloid burden. None of this can be explained by differential survival, because none of these people has died.

The natural experiment that comes closest to a test is in her bibliography, cited for something else. In the Mayo Clinic oophorectomy cohort — 813 unilateral, 676 bilateral, 1,472 matched referents — removal of the ovaries before natural menopause raised the hazard of cognitive impairment or dementia to 1.46 (95% CI 1.13–1.90), with risk rising the younger the surgery (trend $p < 0.0001$) and the excess largely absent in women given oestrogen until age 50. In UK Biobank, natural menopause before 47 carried a hazard of 1.32 (1.15–1.51) against menopause at 50, and hysterectomy with prior oophorectomy 2.35 (1.06–5.23). This is a dose–timing–outcome triad in humans and it is the best evidence her theory has. The submission cites the review that reports it in support of a general remark about treatment timing.

The therapeutic record is where the theory earns a partial acquittal and takes a real wound. Her framework predicts three things about hormone therapy: that the progestogen matters, that early initiation matters, and that late initiation is useless or harmful. The first two are confirmed in observational data — in a meta-analysis of 45 observational reports, oestrogen-only therapy carried a relative risk of 0.86 while oestrogen-plus-progestogen carried 0.91 and was not significant, and midlife oestrogen-only therapy carried 0.685 for dementia, a 32 per cent reduction. The third is confirmed emphatically: in randomised trials in women aged 65 and over the pooled relative risk of dementia was 1.38, driven by combined therapy at 1.64; in the trial that produced that signal, conjugated equine oestrogen with medroxyprogesterone acetate doubled probable dementia (hazard ratio 2.05, 95% CI 1.21–3.48).

And then the randomised test of the timing hypothesis was run, and it was null. In 567 women randomised to oral 17β-oestradiol or placebo — half within six years of menopause, half ten or more years after — the difference in verbal memory after a mean of 57 months was −0.06 (95% CI −0.22 to 0.09), and the interaction between treatment and proximity to menopause had a p value of 0.88. The parallel early-postmenopause trial found no cognitive benefit at four years, and its ten-year observational continuation found none either. A Danish national register found *elevated* dementia rates with combined therapy that persisted among women treated at 55 or younger, with a duration–response gradient reaching 1.74 above twelve years. The submission does not cite the timing trial. It cites its first author, for a review of mitochondria.

The defence available to the theory is real, and it is a defence about endpoints rather than about effects. Eckert's own staging says that the years after menopause are a *plateau* — a new equilibrium at lower throughput in which cognition is preserved. A trial that enrols women in early post-menopause and measures verbal memory for four years is measuring the one variable her model predicts will not move. The endpoint her framework demands is metabolic: cerebral glucose utilisation and the substrate the brain has switched to. That prediction is not vague, and it has never been the primary outcome of a hormone trial.

The idea worth keeping is the one she states in a single paragraph. Her model has two branches. In the first, the brain meets the withdrawal by switching fuels and ages without dementia. In the second, the switch fails and the metabolism collapses. Every woman is exposed; most do not get the disease; therefore the disease cannot be the exposure. On her own account, what separates the two groups is *the success of a compensation* — which converts a hormone-deficiency theory into a resilience theory with a named mechanism and a dated window. She does not press this, and it is the most useful thing in the paper.

The compensation has since been imaged in humans, one year after the submission. A multimodality study of the menopause transition reported that brain biomarkers largely stabilised after menopause, that grey matter volume recovered in key regions, and that this recovery and in vivo brain ATP production correlated with preservation of cognitive performance — described by its authors as "adaptive compensatory processes." That is

Eckert's Figure 5, in living women, published after she predicted it.

The compensation is also, in part, a lesion. In the ageing female rodent brain the alternative fuel is generated by catabolising the brain's own myelin: cytosolic phospholipase A2 and sphingomyelinase activation, electron-microscopic and lipidomic confirmation of myelin degeneration, a rise in brain ketones against a fall in plasma ketones. The successful adaptation is a trade, and what it trades away is white matter. This both strengthens the theory — it explains why white-matter change appears on this schedule — and complicates its therapeutic reading, since supplying ketones exogenously is then not merely a substitute fuel but a way of buying back myelin.

The pharmacology of the switch is favourable and under-exploited. In mild Alzheimer's dementia, global grey matter glucose metabolism is about 13 per cent below that of age-matched controls, while the cerebral metabolic rate and rate constant for acetoacetate are statistically indistinguishable from normal. The glucose door is closing while the ketone door stands open. A six-month randomised trial of a ketogenic medium-chain triglyceride drink in mild cognitive impairment improved free and cued recall, verbal fluency, naming and executive error rate, with effects correlating with achieved plasma ketone levels. Of the four interventions Eckert proposes, this is the one with the best evidence and the least attention in her own text.

Three problems the theory does not solve, and one it does not acknowledge. It has no account of the male third of the disease; the natural experiment for that — abrupt androgen withdrawal in men treated for prostate cancer, where two large studies report hazard ratios near 1.7–1.9 — is neither cited nor discussed, and the theory makes a clear prediction about it. Its central cascade is not new: a mitochondrial-cascade hypothesis for sporadic Alzheimer's disease was published in 2004 and is absent from the bibliography, which leaves the paper claiming novelty for the cascade when its novelty is the trigger. Bioenergetic failure is not menopause-specific — young *APOE* ε4 carriers aged 20 to 39 already show the regional hypometabolic pattern, three decades before any endocrine transition. And the framework risks a circularity that must be watched: hypometabolism is proposed as the cause of the disease and used as the measure of it.

Where this leaves the argument. We grade twenty-four claims, of which nine are established, eight are supported but unproven, four are unsupported as stated, and three are contradicted by evidence available when the paper was written. We propose a reformulation that keeps the mechanism and discards the over-reach: the menopause is not a cause of Alzheimer's disease but a *scheduled, universal bioenergetic stress test*, administered to half the population at a known date, whose outcome is determined by reserve the patient already had. On that reading the target is not the hormone. It is the switch.

We close with five conditions that would refute the reformulated theory and ten experiments in rank order. The first has never been done and needs no new technology: measure whether the age at which a woman's symptoms begin tracks the age at which her menstrual cycles ended. If the clock is menopausal, that slope is positive. If it is not, the whole timing argument is a

coincidence of medians, and the field should stop repeating it.

Part I — The Claim and the Programme Behind It

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 she does.

The proposition is that Alzheimer's disease in women has an entry point, that the entry point is the menopause, and that the mechanism of entry is bioenergetic. The argument proceeds in five movements.

The organ movement. The brain consumes roughly a fifth of the body's basal oxygen. It is post-mitotic, so its cells are not replaced when damaged; it is electrically excitable, so a large fraction of its energy budget goes to restoring ion gradients after every action potential; and it is exceedingly compartmentalised, so energy must be delivered not merely to cells but to positions within cells — to a synapse at the end of an axon a thousand times longer than the cell body is wide. Neurons cannot switch to fatty acid oxidation as a routine fuel: the ATP generation rate is too slow for their demand and the radical yield too high. They are therefore committed, more completely than any other tissue, to mitochondrial oxidative phosphorylation running on glucose. A tissue with no fuel flexibility, no cell replacement and no tolerance for interruption is a tissue in which a chronic energy shortfall will show first.

The ageing movement. With age, that system degrades in three coordinated ways: antioxidant defences fall, oxidative damage accumulates, and oxidative phosphorylation loses capacity. Post-mortem human hippocampus and frontal cortex show a progressive age-related rise in oxidative damage alongside falling superoxide dismutase, catalase and glutathione reductase activity and falling complex I activity. In vivo spectroscopy shows glutathione content declining between the third and sixth decades. Cerebrospinal-fluid F2-isoprostane, an index of free-radical injury, rises about 10 per cent between ages 45 and 71 in cognitively normal, medically healthy adults — and rises further in smokers and in those with high body mass index, which is the paper's quiet reminder that this is a modifiable curve.

The convergence movement. The two proteins of Alzheimer's disease meet on this system. Reactive oxygen species promote amyloidogenic processing of the amyloid precursor protein; mice lacking superoxide dismutase 2 show increased tau and increased tau phosphorylation; and both proteins in turn degrade respiration. Eckert's claim is not that this is a loose association but that it is a closed loop, and that the loop is entered from the energetic side in sporadic disease. Her own laboratory supplies both arrows, and we take that up in Part II.

The sex movement. Young women are metabolically better defended than young men — higher brain glutathione in frontal and parietal cortex, lower mitochondrial peroxide production, higher glutathione peroxidase and cytochrome oxidase activity in rodent brain. The advantage is attributed to oestradiol, which increases glucose transport and glycolytic and Krebs-cycle gene expression, upregulates oxidative phosphorylation components, raises superoxide dismutase and glutathione, and modulates cellular redox state through several signalling routes. It follows that the advantage ends when the hormone does — and that its ending is not gradual. In men, gonadal steroid decline is a slow slope across decades. In women it is a step.

The staging movement, and the conclusion. Because the loss is a step, the brain must respond to it as an event. Eckert proposes that it does, and that the response has two possible outcomes.

> *In the first, "a successful bioenergetic shift occurs at the peri-menopause with the activation of metabolism for alternative energy substrates in the brain" — a compensation that maintains adequate ATP production and offsets the deficit created by hormone loss. In the second, "the brain fails to perform this bioenergetic shift, leading to the collapse of brain metabolic activity and, consequently, to neuronal death and cognitive impairments."*

Where the second branch is taken, the paper proposes that the progression runs through three stages: an attempt at metabolic adaptation at the peri-menopause; a stable metabolic phase in the early post-menopause, at reduced throughput but sufficient for near-normal function, which she identifies with the prodrome or mild cognitive impairment; and a hypometabolic phase in the late post-menopause in which the equilibrium collapses, neurons die, and dementia follows.

Two features of this argument deserve to be noticed before it is examined, because both are unusual and both are load-bearing.

The first is that **the causal claim is about a date, not only about a molecule.** Most theories of Alzheimer's disease specify a lesion and leave the timing to be inferred. This one specifies an event with a calendar age and derives the lesion from it. That makes the theory testable in a way that most are not, and it also makes it vulnerable in a way most are not: if the date is wrong, the theory is wrong, and the date is measurable in every woman who has ever been asked when her periods stopped.

The second is that **the theory is, formally, a theory of failed compensation rather than a theory of injury.** The injury is universal. Every woman undergoes the menopause; every woman's brain loses the same regulator. The disease is defined, on this account, by what happens next. We will argue in Part IV that this is the most important idea in the paper and that its author underuses it.

2. The Author: What the Publication Record Actually Shows

The submission reads, at first pass, as a review — a survey of mitochondria, ageing, sex hormones and diet, assembled from other people's findings and pointed at a hypothesis in the last two pages. That reading is wrong, and correcting it changes how the paper should be weighted.

Anne Eckert is a pharmacologist and neurobiologist based at the Neurobiology Laboratory for Brain Aging and Mental Health of the Psychiatric University Clinics Basel, with the Research Cluster Molecular and Cognitive Neuroscience in the Department of Biomedicine at the University of Basel. Her indexed record runs from the 1990s to the present and divides cleanly into two programmes that the submission is an attempt to join.

The first programme is about the organelle and the two proteins. It begins in Frankfurt in Walter Müller's department and continues in Basel. Its primary papers are experimental, not review: proteomic and functional analysis of mitochondria in P301L tau transgenic mice, with confirmation of the key proteomic finding in human frontotemporal dementia brain tissue; comparison of oligomeric, fibrillar and disaggregated amyloid-β preparations against mitochondrial membrane potential in cortical cells from those mice; an isobaric-tag proteomic screen across 1,275 proteins in triple-transgenic animals carrying both pathologies; a cell model dissecting the effect of wild-type against mutant tau on complex I activity and on fission and fusion machinery; and, in collaboration, a mouse cross designed to test whether the causal arrow runs backwards as well as forwards. This is a laboratory that measures respiration, membrane potential and ATP in defined genetic backgrounds. Its conclusions about the respiratory chain are its own.

The second programme is about steroids and bioenergetics. With Amandine Grimm and Ayikoe-Guy Mensah-Nyagan it produced a series on neurosteroids and neuronal energy metabolism, on oestrogen and mitochondria, and on sex as a variable in mitochondrial ageing. The series is largely review and cell-model work rather than in vivo endocrinology, and it draws heavily — and explicitly — on Roberta Diaz Brinton's programme in Southern California, which supplies most of the animal and much of the human material on the perimenopausal metabolic transition. It is important to be exact about this: the perimenopausal bioenergetic shift is Brinton's discovery. Eckert's contribution to that idea is to weld it to a mitochondrial-lesion programme of her own and to state the result as a staged theory of disease.

The programme has continued past the submission and in the direction the submission indicated. Since 2020 the laboratory has published on tau and mitophagy, on

spermidine rescuing bioenergetic and mitophagy deficits in a tauopathy cell model, on translocator-protein ligands and mitochondrial quality control, on mitochondrial transplantation into tau-expressing cells, and — most pointedly — on estetrol, a fetal oestrogen with a selective receptor profile, which raised ATP, membrane potential and respiration in amyloid and tauopathy cell models and outperformed 17β-oestradiol in the P301L line. The last of these is the submission's therapeutic proposal being pursued with a different molecule, chosen to avoid the thrombotic and oncological liabilities that sank conventional hormone therapy. Whatever one concludes about the 2020 paper, its author did not treat it as a closing statement.

Three consequences follow for how the submission should be read.

First, the mitochondrial sections are not a survey; they are her subject. When the paper asserts that bioenergetic deficits precede plaques and tangles, that assertion rests in part on her own animal work, and it should be graded as primary evidence with the usual model-organism discount rather than as a citation of consensus.

Second, the endocrine sections are a synthesis of someone else's programme, competently done and honestly attributed in the bibliography, but not independent evidence in the sense the mitochondrial sections are. When the two are combined into a theory, the joint carries the weaker of the two warrants.

Third, the therapeutic section is a pharmacologist's section, and it shows. It is the only part of the paper that lists compounds, doses of a sort, timing regimens and a staged clinical protocol. It is also the part in which the evidence is thinnest and the reach longest, and we grade it accordingly in Part V.

3. What Kind of Claim This Is

Theories of Alzheimer's disease can be sorted by what they take to be the explanandum. Most take the *pathology* — why is there amyloid, why is there tau — and derive the clinical syndrome from it. A minority take the *syndrome* and treat the pathology as one of its features. Eckert's takes a third thing: the **epidemiological shape** of the disease, and specifically two facts about that shape that most mechanistic theories do not attempt to explain.

The first is that the disease has a long prodrome of roughly fifteen to twenty years, during which biomarkers move and cognition does not. The second is that it is unevenly distributed by sex. Her theory is constructed to explain both at once, and the elegance of the construction is that a single event does the work: menopause is placed at the head of the prodrome, and the prodrome's length becomes the interval between the endocrine transition and the metabolic collapse.

This is worth stating plainly because it determines what would count as a refutation. Three kinds of evidence bear on a claim of this shape, and they are not interchangeable.

Mechanism evidence answers: does oestradiol in fact regulate brain bioenergetics, and does its withdrawal in fact impair them? This is largely settled in the affirmative, in cells and in animals, and Part II and Part III treat it as established.

Timing evidence answers: does the clinical clock actually start at the endocrine event? This is the theory's distinctive claim and the one on which it should be judged. It is weakly supported. What exists is a coincidence of population medians — menopause near 51, symptomatic disease near 70, prodrome estimated at fifteen to twenty years — plus a set of studies showing that biomarkers differ by menopausal stage in cross-section. What does not exist, and what the theory needs, is evidence that *within* women the age at menopause predicts the age at which the disease arrives. We return to this in §9, and it is the first of our proposed experiments.

Outcome evidence answers: does restoring or replacing the missing input change the disease? Here the theory has made specific predictions, and the record is mixed in an instructive way: the predictions about *which* hormone and *when* are borne out observationally and the predictions about *effect on cognition* are not borne out in randomised trials. Part V takes this apart.

A final point of method. This paper grades claims by the strength of the evidence available for them, on a three-level scale used throughout:

Grade	Meaning
Established	Replicated in humans, or in humans and animals, by independent groups; the claim would require substantial new contrary data to overturn.
Supported	Consistent evidence exists but is confined to one species, one design, one laboratory, or to cross-sectional association where a longitudinal test is possible and has not been done.
Unsupported	Asserted without adequate evidence, or contradicted by evidence available at the time of assertion. Not the same as *false*: several unsupported claims here are probably true and simply have not been tested.

Grading is applied to propositions, not to people, and a theory containing unsupported claims is not thereby refuted. The purpose is to say precisely where the argument is carrying weight it has not earned, so that the parts that have earned it can be used with confidence.

Part II — The Organelle: What the Laboratory Established

4. Tau at Complex I

The programme begins in 2005 with a proteomic screen that was not designed to find a bioenergetic answer and found one.

Mice overexpressing the P301L mutation of human tau — the mutation that causes frontotemporal dementia with parkinsonism linked to chromosome 17, and the workhorse strain for modelling tangle formation — were profiled by two-dimensional gel proteomics and the differing spots identified. The proteins that came up were metabolic: respiratory-chain components, antioxidant enzymes and synaptic proteins. The finding was then taken out of the mouse and checked in people. The reduction in complex V that the proteomics had flagged was confirmed as reduced in human P301L frontotemporal dementia brain. Functional assays in the mice showed reduced NADH-ubiquinone oxidoreductase activity — complex I — and, with age, impaired respiration and impaired ATP synthesis, accompanied by higher reactive oxygen species in the aged animals.

Three things are worth noting about this first paper, because they set the standard the rest of the programme is held to.

It was **discovery-driven rather than hypothesis-confirming**: nobody screening a tau mouse in 2004 expected the answer to be the electron transport chain, and the finding is correspondingly harder to explain as bias.

It was **cross-validated in human tissue**, which most mouse mitochondrial work is not.

And it was **age-dependent** — respiration and ATP synthesis failed in older animals, not in young ones. That is the correct shape for a claim about a degenerative disease, and it is a shape that can fail: a lesion present at birth in a transgenic line tells you about the transgene, not about ageing.

Seven years later, the mechanism was resolved in a cell model that separated the mutation from the protein. Human neuroblastoma lines stably overexpressing either wild-type or P301L tau were compared. The P301L line showed a substantial complex I deficit, lower ATP, and greater susceptibility to oxidative challenge, with pronounced changes in mitochondrial morphology: reduced fusion and reduced fission, and lower expression of the machinery that performs them, including OPA1 and DRP1. The mitochondrial network in a tauopathy cell is not merely underpowered; it is frozen — unable to fuse damaged units into functional ones or to divide them for disposal.

And the wild-type line went the other way. Overexpressing normal tau *improved* mitochondrial function and dynamics, including *enhanced* complex I activity. The paper's own summary is that the findings "clearly link tau bidirectionally to mitochondrial function."

We think this is the most under-exploited result in the entire programme, and we return to it in §29. If normal tau positively regulates complex I, then three things follow that the field has not absorbed. Tauopathy involves the loss of a normal function and not only the gain of an abnormal one, which means a mouse that models the gain will systematically understate the deficit. The observed complex I loss in disease is then the sum of two effects working in the same direction — mutant tau doing harm and normal tau being withdrawn from its job — which predicts a non-linear relation between tau burden and respiratory deficit. And any therapeutic strategy that lowers *total* tau, as several antisense and immunotherapeutic approaches do, is removing a protein that the mitochondrion was using, at a dose that is not titrated against that function because nobody is measuring it.

Grade: established for the mutant-tau complex I deficit, replicated in mouse and cell and consistent with human post-mortem enzyme data. **Grade: supported** for the wild-type tau enhancement, which rests on one cell model from one group and needs replication in neurons and in vivo. That replication has not, to our reading, been done in the fourteen years since.

5. Amyloid at Complex IV, and the Synergy

The second half of the mechanism arrived in 2009, in the paper that is the programme's strongest single contribution.

Two mouse lines were crossed: the P301L tau line, which makes tangles, and an APP~swe~/PS2~N141I~ double transgenic, which makes amyloid plaques. The cross yields animals carrying both pathologies. Vesicular preparations from the triple-transgenic mice, from both parental strains and from non-transgenic controls were run through isobaric-tag quantitative proteomics and mass spectrometry. Of 1,275 quantified proteins, 24 were massively deregulated, and a third of those were mitochondrial and belonged mainly to complexes I and IV of the oxidative phosphorylation system.

Then came the dissociation, and it is worth quoting the finding in the authors' own terms: deregulation of complex I was **tau dependent**, whereas deregulation of complex IV was **amyloid-β dependent**, "both at the protein and activity levels."

This is a different order of claim from the usual statement that mitochondria are impaired in Alzheimer's disease. It says the two pathologies are not redundant, that they attack different components of the same machine, and that the attribution can be made by genotype. It is also the kind of claim that could have failed cleanly and did not.

The synergy claim followed from the same experiment. At eight months, only the triple-transgenic animals showed a reduction in mitochondrial membrane potential; neither single-pathology parent did at that age. Two sub-threshold lesions at different complexes produced a supra-threshold failure of the membrane potential that both complexes serve. This is what a convergence hypothesis should look like when it is right: not "both things are bad" but "each thing does something specific and the specifics interact."

A companion study addressed which amyloid species does the damage. Oligomeric and fibrillar amyloid-β~42~ both lowered mitochondrial membrane potential in cortical cells from P301L mice; disaggregated, largely monomeric preparations did not. The effect was absent in cerebellar preparations, which is a regional-vulnerability control that most such experiments omit.

How well does the dissociation hold up in human tissue? Partly, and asymmetrically, and this must be said plainly.

The complex IV limb is on firm human ground. Cytochrome oxidase activity is reduced by 25–30 per cent in frontal, temporal, parietal and occipital cortex in Alzheimer's disease against age-matched controls, and in the same study complexes I and II–III showed only a small decrease confined to occipital cortex. That is a human post-mortem result from an independent group, and it is a good fit to an amyloid-driven complex IV lesion in a disease defined by amyloid.

The complex I limb is on weaker human ground, and the same study is the reason. If tau drives a complex I deficit and tau burden in Alzheimer's cortex is severe, one would expect a measurable cortical complex I deficit, and the most-cited survey of respiratory-chain activities in Alzheimer's cortex did not find one outside occipital cortex. Human mitochondrial enzymology in Alzheimer's brain finds its most consistent abnormalities elsewhere in the metabolic apparatus: pyruvate dehydrogenase down 41 per cent, isocitrate dehydrogenase down 27 per cent, and the α-ketoglutarate dehydrogenase complex down 57 per cent, with succinate dehydrogenase and malate dehydrogenase *increased*, and all of these correlating with clinical state before death. That is a lesion in the tricarboxylic acid cycle and in the pyruvate gateway into it — upstream of the respiratory chain, on the fuel-handling side rather than the electron-transport side.

We do not read this as refuting the dissociation. Post-mortem enzymology in end-stage brain measures a system that has been remodelling for years, and the mouse experiment measures a defined genotype at a defined age. But the honest grading is:

Grade: established for the tau/complex I and amyloid/complex IV dissociation *in the mouse*, which is a clean, replicable, well-controlled result. **Grade: supported** for its extension to human disease on the complex IV side. **Grade: unsupported** for its extension to human disease on the complex I side, where the available cortical enzymology does not show the predicted deficit and the dominant human abnormality is in the TCA cycle rather than in complex I. The submission does not distinguish these, and it should.

6. The Return Arrow: Making Mitochondria Fail First

Every mitochondrial account of neurodegeneration invokes a vicious cycle. Almost none of them demonstrate the second arrow. If damaged mitochondria are downstream of the proteinopathy, they are an epiphenomenon of clinical interest but no causal standing. The question is whether starting at the organelle produces the disease.

Two independent bodies of work say it does, and the first is a collaboration Eckert took part in.

The Harlequin cross. The Harlequin mouse carries a proviral insertion that greatly reduces expression of apoptosis-inducing factor, a mitochondrial flavoprotein; the animals suffer mitochondrial dysfunction and oxidative stress and degenerate progressively. Crossing this line into P301L tau transgenics produced double mutants with *more* tau pathology and *more* apoptotic neurodegeneration than either single mutation, most prominently in the dentate gyrus, with degeneration also significantly increased in the cerebellum and consequent motor deficits. Respiratory-chain measurements in the double mutants confirmed the compounded mitochondrial lesion.

This is the return arrow demonstrated in a mammal. A primary, genetically defined mitochondrial insult increases tau pathology. It does not, by itself, prove that this is how sporadic human disease begins — the insult is a null allele, not an age-related decline — but it removes the possibility that mitochondrial failure is merely a consequence.

The complex I inhibitor, and a human population. The second body of work is independent of Eckert's group and is, we think, stronger.

On Guadeloupe, an unusual concentration of atypical parkinsonism with tau pathology was associated in a case–control study with consumption of fruit and herbal tea from Annonaceae, plants that contain acetogenins — potent lipophilic inhibitors of mitochondrial complex I. The prototypical acetogenin, annonacin, was then applied to primary striatal neurons. It produced a concentration-dependent fall in ATP, a redistribution of tau from axons to the cell body, retrograde transport of mitochondria with tau attached to their outer membranes, and cell death.

The rescue experiments are what make this study important, and they cut against a central assumption of the framework under review. Antioxidants, which scavenged the reactive oxygen species produced by complex I inhibition, did **not** prevent either the tau redistribution or the cell death. What did prevent both was forced expression of NDI1, the yeast NADH-quinone

oxidoreductase, which restores NADH oxidation in complex I-deficient mammalian cells without restoring anything about the radical chemistry.

The tau consequence of complex I inhibition is therefore carried by the **energy deficit**, not by the **oxidative stress**. Eckert's framework routes nearly everything through reactive oxygen species: the free-radical theory of ageing supplies its opening frame, oxidative stress supplies its link to amyloidogenic processing, and antioxidants supply a large part of its therapeutic programme. The annonacin experiment says that at least one of the two arrows runs on ATP rather than on radicals, and that antioxidants applied to that arm will fail. This is a mechanistic warning that the paper's therapeutic section needed and did not receive.

Grade: established that a primary mitochondrial lesion increases tau pathology, in two independent systems, with a human epidemiological correlate. **Grade: established** that at least one route from complex I to tau is ATP-dependent rather than radical-dependent. **Grade: unsupported** for the framework's implicit assumption that oxidative stress is the common currency of both arrows.

7. Beyond Bioenergetics: Transport, Dynamics, Mitophagy

A neuron is not a bag of mitochondria. It is a structure in which mitochondria must be manufactured centrally, trafficked over distances of up to a metre in the human peripheral nervous system and several centimetres in the brain, positioned at synapses whose demand fluctuates on a millisecond timescale, fused with one another to share contents, divided for quality control, and destroyed when irreparable. Any of these can fail independently of respiratory capacity, and the tau literature now implicates all of them.

The laboratory's own review of this territory sets out the inventory: disease-associated tau impairs mitochondrial transport, network dynamics, mitophagy and bioenergetics, interacts directly with mitochondrial proteins, and — in an observation that connects the two halves of the submission — affects mitochondrial neurosteroidogenesis and endoplasmic reticulum–mitochondria coupling.

That last point deserves emphasis because it is the mechanistic bridge the submission needed and did not build. Neurosteroid synthesis begins in the mitochondrion: cholesterol import across the outer membrane is the rate-limiting step, and the machinery that performs it sits in the same membrane system the disease is damaging. If tau impairs mitochondrial neurosteroidogenesis, then the relationship between steroids and mitochondria in Alzheimer's disease is not a one-way street in which hormone loss damages the organelle. It is a loop in which organelle damage also reduces the brain's own capacity to make the steroids that protect it. A woman who reaches menopause with an already-compromised mitochondrial population loses the systemic hormone *and* the local capacity to compensate for its loss. The submission asserts the first half of that loop and possesses, in its own authors' review literature, the second.

The subsequent work has pursued the quality-control arm directly. Spermidine, a polyamine and autophagy inducer, rescued bioenergetic and mitophagy deficits in the tauopathy cell model. Ligands of the translocator protein — an outer-membrane protein upregulated in Alzheimer's disease and best known as a PET marker of neuroinflammation — attenuated mitophagy deficits and mitochondrial fragmentation in an amyloid cell model, acting through the autophagy adaptor p62. And in 2025 the laboratory reported that transplanting intact mitochondria isolated from astrocytic cells into tau-expressing neuroblastoma cells raised bioenergetics and restored neurite outgrowth.

The last of these is worth pausing on as a matter of logic rather than of therapeutics. Mitochondrial transplantation is a long way from a clinical proposition in the brain. But as an experiment it is a clean test of a claim the whole framework depends on: that the bioenergetic deficit is *sufficient* for the cellular phenotype. If replacing the organelle restores the phenotype in a cell that still contains all its pathological tau, then the tau is doing its damage through the mitochondrion rather than around it. That is a strong inference, available cheaply, and it is the right kind of experiment for this programme to be running.

Grade: established that disease-associated tau impairs mitochondrial transport, dynamics and mitophagy. **Grade: supported** for the claim that restoring mitochondrial function is sufficient to reverse the cellular phenotype, resting on cell-model transplantation in one laboratory.

8. What the Animal Work Does and Does Not License

Three discounts must be applied before this body of work is carried into a theory of human disease, and the submission applies none of them.

The first is the mutation discount. Almost the entire tau limb of this programme runs on P301L. That mutation causes frontotemporal dementia, not Alzheimer's disease. It is not found in Alzheimer's patients; it produces a different clinical syndrome, a different regional distribution and a different tau isoform composition. The justification for using it is that it aggregates tau reliably in a mouse, which is a justification about tractability rather than about validity. The finding that P301L tau lowers complex I while wild-type tau raises it makes this discount sharper rather than softer: the two forms of the protein have *opposite* effects on the readout, so the choice of form is not a technical detail. Whether wild-type human tau, hyperphosphorylated as it is in Alzheimer's disease, sits with the mutant or with the normal protein on this axis is an open and important question.

The second is the overexpression discount. These are overexpression models, in cells and in mice. Mitochondrial handling of an overexpressed aggregation-prone protein is a plausible proxy for handling an endogenous one that has begun to aggregate, but it is a proxy, and the failure modes of protein-handling systems are notoriously dose-dependent.

The third is the direction-of-inference discount, and it is the largest. The animal work establishes that these proteins damage mitochondria and that damaged mitochondria worsen these proteinopathies. It does not establish that in sporadic human Alzheimer's disease the sequence begins on the mitochondrial side. Every experiment cited above starts by installing one of the two lesions. None of them starts with normal ageing.

The one piece of human evidence that bears directly on which comes first cuts in an awkward direction for the timing claim. Cognitively normal *APOE* ε4 heterozygotes aged 20 to 39 already show abnormally low glucose metabolism in posterior cingulate, parietal, temporal and prefrontal cortex — the same regions affected in probable Alzheimer's dementia — with no difference from non-carriers in clinical ratings or neuropsychological performance. In that subgroup the hypometabolic signature is present three decades before menopause and five before symptoms.

This does not refute the theory. It refutes one reading of it: that the bioenergetic lesion of Alzheimer's disease *begins* at the endocrine transition. In at least one genetically defined group it begins in early adult life. The defensible version is that the menopause is a large, dated, universal

increment to a bioenergetic burden whose baseline was set earlier by other things — genotype among them. That version survives the Reiman data. The version in which menopause opens the door does not, and the submission's title uses the door.

Grade: established for mitochondrial involvement. **Grade: supported** for bioenergetic deficit as an early event preceding pathology, in mice and in genetically at-risk humans. **Grade: unsupported** for the proposition that the bioenergetic deficit in sporadic disease is initiated by the menopause, as opposed to being augmented by it.

Part III — The Clock: Menopause as a Dated Exposure

9. The Arithmetic of the Interval

The timing argument in the submission occupies a single sentence, and it is the sentence the whole theory turns on:

> *"Strikingly, the age of menopause seems to correspond to the initiation of the 'prodromal phase' of AD, which usually starts 15 to 20 years before the appearance of the first clinical symptoms."*

The arithmetic works. The median age of natural menopause in European and North American populations is close to 51. The paper's own figure legend puts the average age of symptomatic onset at about 70. The interval is nineteen years, which falls inside the fifteen-to-twenty-year prodrome that the preclinical-Alzheimer's literature estimates. Three numbers, and they line up.

We want to be exact about what this observation is worth, because it is repeated widely and it is worth less than it looks.

What it establishes. That the menopause hypothesis is not obviously excluded on timing grounds. This is not nothing. A theory that placed the initiating event at age 30 or at age 68 would be in immediate difficulty, and this one is not.

What it does not establish, and why. The same interval is applied to men. The prodromal interval is not estimated separately by sex — the fifteen-to-twenty-year figure comes from studies that do not stratify — and male symptomatic onset is also in the seventh decade, and men do not undergo a menopause. If a fixed pre-symptomatic interval is a general property of the disease process — which is how the preclinical-Alzheimer's literature treats it — then the coincidence between menopause and the start of the female prodrome is entailed by the arithmetic of medians and carries no information about causation. Subtract twenty from seventy and you get fifty in both sexes. The menopause happens to be there.

This is the most important methodological point in the evaluation, so we state the test that would settle it. **If the clock is menopausal, then within women, the age at symptomatic onset should track the age at final menstrual period with a slope approaching one.** A woman whose menses ended at 42 should reach symptoms about nine years before a woman whose menses ended at 51, other things equal. If the slope is flat — if onset age is the same regardless of when the transition occurred — then the interval is a property of the disease and not of the endocrine event, and the coincidence of medians is a coincidence.

To our reading, that regression has never been published. The reproductive-epidemiology literature has repeatedly asked whether early menopause raises *risk*; it has not asked whether age at menopause sets *onset age* in those who go on to develop the disease. The data to do it exist in several longitudinal cohorts. It is the first of the experiments we propose in §32, it requires no new measurement, and it is a genuine falsifier.

Grade: supported that the timing of menopause is compatible with the observed prodromal interval. **Grade: unsupported** that the coincidence of medians is evidence for a menopausal clock, since the identical interval holds in a sex that has no menopause.

10. The Premise the Paper Leads With, and Why It Does Not Support the Theory

The submission opens its epidemiological case as follows: "Epidemiological studies showed that women represent two-thirds of AD patients." Later it returns to the point and dismisses the obvious alternative:

> *"The prevailing, and rather simplistic, explanation why the disease seems to affect more women than men proposes that women live longer on average. However, increasing evidence indicates a 'biological underpinning' for the gender difference in the disease."*

The conclusion is defensible. The route taken to it is not, and three of the paper's own citations say so.

The review cited for the two-thirds figure gives competing mortality as its leading explanation. The source is a clinical-epidemiology review whose abstract states that "men may have a higher risk of mild cognitive impairment," that women are disproportionately affected with Alzheimer's disease, and that "one explanation is that men may die of competing causes of death earlier in life, so that only the most resilient men may survive to older ages." That is the survival explanation, stated first, by the authors of the paper being cited to establish the premise that the survival explanation is simplistic.

The incidence study cited for a post-80 sex difference attributes it to survival in its own abstract. The submission reports that "after 80 years of age, a significant difference between the AD incidence rate in men and women was confirmed by a recent large study including 16,926 subjects." The study is a twin-registry analysis of 16,926 women and men aged 65 and over. It did find higher incidence in women, with any-dementia rates diverging after 85 and Alzheimer's rates around 80. And it concludes, in its own words, that "this pattern is consistent with women's survival to older ages compared to men."

The best mid-life-onward cohort finds cumulative incidence similar. In the Framingham Heart Study, followed prospectively with cause-specific mortality ascertained — 777 incident dementia cases, 601 of them Alzheimer's, in 7,901 participants over 136,266 person-years — *cumulative incidences were similar in women and men*. What differed was lifetime risk after 85, and lifetime risk is by construction a survival-weighted quantity: 1 in 5 for women at age 45 against 1 in 10 for men. The authors offer selective survival of cardiovascularly healthier men as a partial explanation.

The correct statement, then, is this. **The two-thirds figure is a prevalence figure. Prevalence is incidence multiplied by duration and filtered through who is alive to be counted. It cannot, by itself, distinguish a female-specific mechanism from a male-specific competing mortality, and the studies Eckert cites for it say so.**

We want to be scrupulous about what this does and does not damage. It does not damage the theory. A sex-specific biological mechanism can be entirely real and still not show up as a net incidence difference, if it is offset by men's higher vascular and mortality burden — indeed a theory that predicted a large net female excess in age-specific incidence would now be in trouble, because that excess is not reliably observed. What it damages is the *argument as presented*: the paper leads with its weakest evidence, dismisses the standard alternative explanation without engaging it, and cites three sources that endorse the alternative.

There is a further irony in the paper's own text, and to its credit it reports it. Women may be *under*-diagnosed at the early stage, because they outperform men on the verbal memory tests used to define amnestic mild cognitive impairment; re-norming those tests by sex reclassified 10 per cent more women and 10 per cent fewer men into the diagnosis. If that is right, it is an argument that the observed female excess in diagnosed disease is partly a measurement artefact operating in the *opposite* direction to the survival artefact — and the paper offers both without noticing that they are two reasons to distrust the headcount it opened with.

Grade: established that women constitute roughly two-thirds of prevalent Alzheimer's cases in the United States and Europe. **Grade: unsupported** that this prevalence ratio demonstrates a female-specific biological mechanism. **Grade: established** that sex-specific norming of verbal memory tests changes the diagnostic distribution substantially.

11. The Biomarker Case, Which Is Much Stronger

The evidence Eckert uses second is far better than the evidence she uses first, and it has the decisive advantage that it cannot be produced by differential mortality: everyone in these studies is alive, cognitively normal, and in midlife.

Graded abnormality across the transition. In forty-three clinically and cognitively normal women aged 40 to 60, staged as pre-menopausal (n = 15), peri-menopausal (n = 14) and post-menopausal (n = 14), fluorodeoxyglucose PET showed reduced cerebral glucose metabolism in Alzheimer-vulnerable regions in both the peri- and post-menopausal groups, alongside platelet cytochrome oxidase activity measured in the same participants. A parallel multimodality study of forty-two women and eighteen age- and education-matched men found hypometabolism, increased amyloid deposition and reduced grey and white matter volume in Alzheimer-vulnerable regions in peri- and post-menopausal women relative to pre-menopausal women *and to men*, controlling for age — with abnormality greatest in the post-menopausal group, intermediate in the peri-menopausal group, and least in controls.

The design feature that matters here is the age-matched male comparison. It is what separates an *endocrine* effect from a *chronological* one. A cross-sectional comparison of pre- against post-menopausal women confounds the transition with being nine years older. Including men of the same ages, in whom nothing endocrine has happened, removes that confound. Both studies did this, and the effect survived.

The larger replication, and the ranking of predictors. In 121 cognitively normal participants aged 40 to 65 — 85 women, 36 men — women showed higher amyloid deposition, lower glucose metabolism and lower grey and white matter volumes than men, with all comparisons corrected for multiple testing and robust to age matching. Men showed no biomarker abnormality relative to women in any modality. When a large set of clinical, medical, hormonal and lifestyle risk factors was entered together, the predictor most consistently and strongly associated with the sex difference, after female sex itself, was **menopausal status** — followed by hormone therapy use, hysterectomy status and thyroid disease. That ranking is the single most useful piece of human evidence for the theory, because it is a competition between candidate explanations rather than a demonstration that one candidate correlates.

The tau finding, and a citation that should be corrected. The submission states that "women with MCI present more diffuse and spread out tau pathology than men," citing a PET

study. The study cited examined *clinically normal* older adults, not people with mild cognitive impairment, across two independent cohorts of 193 and 103 participants; it reported that there was no clear main association of sex with regional tau that replicated across studies, but that in both cohorts women showed higher **entorhinal** tau than men, an effect concentrated in individuals with higher amyloid burden. The finding is focal, not diffuse, and it is in cognitively normal people, not in mild cognitive impairment.

We report the discrepancy because accuracy about a source is not optional, and we note immediately that the correction **strengthens** the theory rather than weakening it. A focal entorhinal excess in cognitively normal women at a given amyloid burden is a cleaner sex-specific vulnerability signal than a diffuse excess in an already-symptomatic group, because the diffuse-in-MCI version could be a consequence of longer undiagnosed disease — which, given the verbal-memory norming problem described above, is exactly what one would expect in women. Eckert had the better result and described the weaker one.

Grade: established that cognitively normal peri- and post-menopausal women show hypometabolism, higher amyloid and lower regional volumes than pre-menopausal women and than age-matched men. **Grade: established** that menopausal status outranks other measured hormonal, medical and lifestyle factors as a correlate of those differences. **Grade: supported** for a female excess of entorhinal tau at a given amyloid burden, replicated across two cohorts but modest in size.

12. The Natural Experiments: What Removing the Ovaries Shows

If the loss of ovarian steroids drives a bioenergetic lesion, then removing the ovaries early should reproduce the lesion early, removing them later should matter less, and replacing the hormone until the age at which it would naturally have gone should abolish the effect. That is a three-part prediction, and all three parts have been tested in humans.

The oophorectomy cohort. In a population-based cohort from Olmsted County, Minnesota, every woman who underwent unilateral or bilateral oophorectomy before the onset of menopause for a non-cancer indication between 1950 and 1987 was identified and matched by age to a referent from the same population: 813 unilateral, 676 bilateral, 1,472 referents. Women who underwent either procedure before menopause had an increased risk of subsequent cognitive impairment or dementia, hazard ratio 1.46 (95% CI 1.13–1.90), adjusted for education, interview type and depression history. The risk rose the younger the woman was at surgery, with a test for linear trend at $p < 0.0001$. The associations held regardless of the indication for surgery, and separately for unilateral and bilateral procedures.

The replacement arm. Re-analysis of the same cohort against the wider literature found evidence for "a sizeable neuroprotective effect of estrogen before age 50 years" in the comparison of bilateral oophorectomy against referent women — that is, the excess risk was concentrated in women who did *not* receive oestrogen up to the age of natural menopause. The same review sets this against the trial evidence at the other end of the window, where initiation at ages 65 to 79 increased dementia risk.

The population-scale replication. In UK Biobank, with 273,240 women followed a median of 11.8 years and 1,866 incident dementia cases, natural menopause before 47 carried a hazard of 1.32 (95% CI 1.15–1.51) against menopause at 50. Hysterectomy carried 1.12 (1.01–1.25). Hysterectomy with previous oophorectomy carried 2.35 (1.06–5.23) — the largest reproductive hazard in the analysis, on the smallest numbers, with correspondingly wide confidence limits.

Taken together this is a dose–timing–outcome triad in humans: earlier loss, larger effect; hormone restored to the natural age, effect largely abolished. It is the strongest evidence the theory has, and it is stronger than anything in the mechanistic literature because it is human, prospective in the Biobank case, and interventional in one arm by accident of clinical practice.

Two cautions, both real. Oophorectomy before natural menopause for a non-cancer indication is not randomly assigned; the indications — endometriosis, fibroids, chronic pelvic pain, prophylaxis in familial risk — carry their own correlates, and while the Mayo analysis found effects independent of indication, indication was recorded rather than randomised. And the Biobank reproductive variables are self-reported, with the usual recall problems around a transition that is often gradual and sometimes surgically obscured.

A finding that does not fit the simplest version of the theory, and should be stated. The same Biobank analysis found a **U-shaped** relation between age at menarche and dementia: hazard 1.20 (1.08–1.34) for menarche before 12 and 1.19 (1.07–1.34) for menarche after 14, against menarche at 13. A pure cumulative-oestrogen-exposure model predicts a monotone relation — earlier menarche means longer exposure means lower risk — and gets the opposite result at one end. Oral contraceptive use, which suppresses endogenous oestradiol, was associated with *lower* risk, 0.80 (0.72–0.88). The reproductive-history evidence is therefore consistent with a menopause effect and inconsistent with a simple lifetime-exposure account, and the submission, which cites lifetime hormone exposure as the explanation for the reproductive-span findings, does not have the second half of that picture.

Grade: established that oophorectomy before natural menopause raises the risk of subsequent cognitive impairment or dementia, with a dose–response on age at surgery. **Grade: supported** that oestrogen treatment to the age of natural menopause abolishes most of the excess, resting on non-randomised comparison within one cohort. **Grade: established** that natural menopause before 47 carries a modest excess risk. **Grade: unsupported** for a simple cumulative-oestrogen-exposure model of female dementia risk.

13. The Animal Model of the Transition, and What It Adds

The human work above is cross-sectional or observational. The mechanistic claim — that the transition itself, rather than age, drives the metabolic change — needs an experimental system in which the two can be separated, and one exists.

Rat reproductive senescence has stages analogous to the human transition: regular cycling, irregular cycling, and acyclicity. Profiling the female rat brain across these stages produced the theory's cleanest animal support, and it is a result about *separability*.

Gene-expression analysis across the transition indicated **two distinct ageing programmes, one chronological and one endocrine**. A critical period emerged during the endocrine transition from regular to irregular cycling, characterised by a decline in bioenergetic gene expression, and confirmed at three independent levels: fluorodeoxyglucose-PET brain metabolism, mitochondrial function, and long-term potentiation. Upstream regulator analysis pointed at insulin/IGF-1 and AMPK/PGC-1α signalling. The onset of acyclicity was accompanied by a rise in the genes required for an alternative fuel economy.

The follow-up went further, combining transcriptomics with untargeted metabolomics and lipidomics in the same model, and found what it predicted: a dynamic adaptation of the ageing female brain **from glucose-centric metabolism to auxiliary fuel sources including amino acids, fatty acids, lipids and ketone bodies**, with coupling between brain and peripheral metabolic systems shifting from uncoupled to coupled under metabolic stress.

This is the substrate switch that Eckert's Stage I describes, observed directly, with the sequence — amino acids first at the peri-menopausal stage, fatty acids predominant post-menopausally — that the submission reports.

The value of the animal work is that it does the one thing the human work cannot: it dissociates the endocrine clock from the chronological clock inside the same animal. If bioenergetic decline in the female brain were simply ageing, it would track months of life. It tracks cycle status.

The discount. The rat menopause is not the human menopause. Rats undergo a gradual transition to persistent oestrus with continued ovarian steroid production rather than the ovarian failure that defines the human event, and the entire model rests on the claim that the two are functionally comparable — a claim the primary papers make carefully and their citers usually do not. The alternative-fuel findings are also, in the main, the product of a single research programme.

Independent replication of the amino-acid-then-fatty-acid sequence, in another laboratory and preferably another species, is the obvious missing control.

Grade: established in the rat that endocrine and chronological ageing programmes are separable and that a bioenergetic decline tracks the endocrine one. **Grade: supported** for the staged substrate switch, resting largely on one programme. **Grade: supported** for extension of the rodent perimenopausal model to human physiology.

14. What the Clock Is Actually Worth

We can now state precisely what the timing contribution amounts to, because it is easy to overstate in either direction.

The submission claims the menopause is the entry point of the disease. That claim is not established and, on the Reiman data in §8, is probably false as a universal statement: at least one genetically defined group carries the hypometabolic signature from early adult life.

But strip the claim back to what the evidence supports and something valuable remains, and it is something the field has almost nothing else of.

Alzheimer's disease is characterised by a decades-long presymptomatic phase whose beginning cannot be observed. Every marker we have — amyloid PET, tau PET, plasma p-tau, hippocampal volume — dates the process retrospectively, by detecting a quantity that has already accumulated. To know when a person's process started, you must have scanned them before it did, which means scanning everyone.

The menopause is different in kind. It is **an exposure with a date**, self-reported, requiring no instrument, occurring in half the population, occurring in essentially all of that half, and preceding the disease by about the length of the prodrome. Whether or not it initiates anything, it is a stratification variable of unusual quality: it identifies, prospectively and cheaply, a moment at which a large, defined, universal metabolic stressor is applied to a specific brain.

That is the correct reformulation, and we propose it as the version of the theory worth taking forward:

> **The menopause is not a cause of Alzheimer's disease. It is a scheduled, universal bioenergetic stress test, administered to half the population at a known date, whose outcome depends on reserve the patient already had.**

This keeps everything the evidence supports — the metabolic insult, the graded biomarker abnormality, the oophorectomy dose–response, the separable endocrine ageing programme — and discards the step the evidence does not support, which is the claim of initiation. It also relocates the interesting variable, from the stressor to the response. Part IV is about the response.

Part IV — The Compensation: The Idea Worth Keeping

15. The Disease as a Failed Adaptation

The most important paragraph in the submission is the one that sets out two branches, and its author treats it as a summary rather than as the thesis.

Every woman undergoes the menopause. Every woman's brain therefore receives the metabolic insult the theory describes. Most women never become demented. It follows, with no further evidence required, that **the insult cannot be the disease**. Something else decides which exposed brain fails, and Eckert names it: the brain either performs a bioenergetic shift to alternative substrates and ages without dementia, or it fails to perform that shift and collapses.

This is a different kind of theory from the one the paper's title advertises, and a better one. An entry door is a claim about a cause. A branch point is a claim about **resilience** — and it reorganises everything downstream.

It changes what the interesting variable is. Under an entry-door reading, the research programme is to characterise the insult: how much oestradiol, how fast, in which regions. Under a branch-point reading, the insult is a constant and the programme is to characterise the *response*: what determines whether the switch succeeds. Constants do not explain variation. The question is not why women get Alzheimer's disease; it is why *these* women do.

It changes what a biomarker should measure. A cause-oriented programme measures the depth of the deficit. A resilience-oriented programme measures the *adequacy of the compensation* — which is a different quantity and, as we will argue in §18, requires measuring a substrate that no clinical protocol currently images.

It changes when to intervene, and in what. If the disease is the failure of a switch, then the therapeutic target is the switch and the therapeutic window is the interval in which it is being attempted. Supplying the missing hormone is one way to try to prevent the switch being needed. Supplying the alternative fuel directly is a way to make the switch succeed without the hormone. These are different strategies with different windows, and the second is not conditional on the first.

And it changes the theory's relationship to the male half of the disease. A hormone-withdrawal theory is female by construction. A failed-adaptation theory is not: it says the disease is what happens when a brain cannot meet a bioenergetic demand it is asked to meet, and it leaves open what does the asking. In women the asking is done by a scheduled endocrine event. In men it may be done by something slower, or by several things. We take this up in §24.

The submission contains this idea, states it once, draws a figure of it, and then reverts in its conclusion to the language of causation: "the theory of the neuroendocrine and bioenergetic shift elucidates the relation between hormonal changes, bioenergetic adaptation and metabolic response during the progression of AD." That sentence puts hormonal change first. The evidence puts adaptation first.

16. The Second Fuel, and the Door That Stays Open

If the brain is to compensate for a glucose shortfall, it must have something else to burn. What that something is, and whether the machinery to use it survives the disease, are empirical questions with good answers.

What the failing brain stops using. In the ageing female rodent brain, the first thing to go is not oxidative phosphorylation but *glucose delivery and entry*. Across 3 to 15 months, both non-transgenic and triple-transgenic females showed a significant decline in brain glucose transport, detected by FDG-microPET, between 6 and 9 months — just before the transition into reproductive senescence — and sustained thereafter. Neuronal glucose transporter expression fell, hexokinase activity fell, and phosphorylated (inactivated) pyruvate dehydrogenase rose. The gate into the mitochondrion closed before the mitochondrion failed.

Lactate declined in parallel with glucose, which rules it out as the alternative fuel — a useful negative result, since the astrocyte-neuron lactate shuttle is the obvious first candidate and it is not what the brain reaches for here.

What it starts using, and where the two branches separate. In the non-transgenic animals, the adaptive response was a shift to the transport and utilisation of ketone bodies as an alternative fuel. In the triple-transgenic animals, ketone utilisation was already evident at the earliest age examined and *declined thereafter*.

That is Eckert's Figure 5 in a single experiment: one genotype makes the switch and holds it; the other makes it early, exhausts it, and falls off. The comparison is the closest thing in the literature to a direct demonstration of the two-branch model, and — a point we make without inference — it is not in the submission's bibliography.

The larger substrate picture. Combining transcriptomics with untargeted metabolomics and lipidomics across the transition showed the switch is not to a single fuel but to a sequence: amino acids, then fatty acids, then lipids and ketone bodies, with the brain's metabolic coupling to the periphery shifting from uncoupled to coupled under stress. The submission reports the sequence — amino acids to compensate at the peri-menopause, fatty acid metabolism predominant post-menopausally — and this is one of the places where its summary of someone else's programme is exact.

The human fact that makes this therapeutically interesting. If the brain in Alzheimer's disease has a general failure of oxidative metabolism, supplying a different fuel will not help. If it has a *glucose-specific* failure, it will.

The answer is known and it is favourable. In mild Alzheimer's dementia, global grey-matter cerebral metabolic rate of glucose was 13 per cent below that of age- and sex-matched cognitively normal older adults — 34.2 ± 5.0 against 38.3 ± 4.7 μmol/100 g/min — with parietal cortex, posterior cingulate and thalamus most affected. In the same participants, imaged with 11C-acetoacetate, neither the global nor the regional cerebral metabolic rate of acetoacetate, nor its rate constant, differed from controls: all comparisons at $p \geq 0.188$.

The glucose door is closing and the ketone door is standing open. The transport, the enzymes and the oxidative capacity for acetoacetate are intact in a brain that has lost an eighth of its glucose uptake. This is a small study — ten patients against twenty-nine controls — and it should be replicated at scale. But it is the single fact that most justifies the fuel arm of Eckert's therapeutic programme, and, as with the two-branch demonstration, it is not cited in the submission, which reaches the same therapeutic conclusion by a longer and weaker route.

An interpretation of the human enzyme data that we offer as a hypothesis, not a finding. Post-mortem Alzheimer's brain shows a peculiar pattern of tricarboxylic-acid-cycle enzyme changes: pyruvate dehydrogenase down 41 per cent, isocitrate dehydrogenase down 27 per cent, the α-ketoglutarate dehydrogenase complex down 57 per cent — and succinate dehydrogenase *up* 44 per cent and malate dehydrogenase *up* 54 per cent, with all changes correlating with clinical state before death.

Read as a lesion, this is a puzzle: why would two enzymes rise in a failing system? Read as an adaptation, it is what a substrate switch looks like. The enzymes that fall are the ones that handle glucose-derived carbon entering the cycle at the top — pyruvate dehydrogenase is the gateway, and isocitrate and α-ketoglutarate dehydrogenases sit in the span immediately below it. The enzymes that rise are the ones in the lower span, which is where anaplerotic carbon from amino acids arrives: glutamate and glutamine enter as α-ketoglutarate, and branched-chain amino acids enter as succinyl-CoA, below the block.

We are explicit that this is our reading and not the original authors' claim. But it generates a test. If the human Alzheimer's brain is running an attempted substrate switch of the kind the rodent transition studies describe, then the enzymes and transporters of brain branched-chain and glutamate carbon handling should show a coordinated rise on the same schedule, the shift should be more pronounced in women, and it should appear in the peri- and early post-menopausal brain before it appears in disease. None of that has been looked for.

Grade: established that in mild Alzheimer's dementia cerebral glucose metabolism is reduced while ketone metabolism is preserved. **Grade: established** in the rodent model that a ketogenic shift is the adaptive response and that it fails in the Alzheimer's genotype. **Grade: supported** for the amino-acid-then-fatty-acid sequence. **Grade: unsupported**, and offered as a hypothesis, for our reading of the human tricarboxylic-acid enzyme profile as an anaplerotic substrate switch.

17. The Compensation Is Also a Lesion

Here the theory acquires a complication that its author does not draw out and that changes how the second branch should be understood.

Where does the ketogenic fuel come from? In a fasting body, from adipose triglyceride by way of hepatic ketogenesis, delivered to the brain in blood. In the ageing female brain, at least in the rodent, it comes from somewhere much less comfortable.

Investigating white-matter degeneration in the ageing female brain, the key study reported a chain: declining mitochondrial respiration and increased mitochondrial hydrogen peroxide production, activation of the cytosolic phospholipase A2–sphingomyelinase pathway, and myelin degeneration confirmed both by electron microscopy and by lipidomics. Fatty acids rose, the mitochondrial fatty-acid metabolism machinery rose with them, and brain ketone bodies rose — while **plasma** ketone bodies *fell*.

That last detail is what makes the finding what it is. If the ketones were coming from the liver, plasma levels would rise. They fell. The brain was making its own ketogenic substrate, locally, out of the lipid it had, and the lipid it had was myelin. The authors describe it, accurately, as "a systems level adaptive response to address brain fuel and energy demand."

Three consequences follow, and none of them is in the submission.

The successful adaptation is a trade, and the currency is white matter. Eckert's Stage I is described as benign — the brain "seems able to adapt its metabolic activity," and this "helps to maintain a proper metabolic activity, preventing the neuronal death that may result from a lack of energy substrates." If the mechanism of the adaptation is myelin catabolism, then Stage I is not free. It buys grey-matter survival with white-matter integrity, and it does so on exactly the schedule at which white-matter hyperintensities begin to appear in midlife women.

This explains something the theory otherwise leaves unexplained. White-matter change is one of the most consistent findings in the ageing brain and one of the least well accounted for by protein-centred theories of Alzheimer's disease. A theory in which the ageing female brain deliberately catabolises myelin for fuel predicts white-matter change as a *consequence of the compensation*, on the endocrine clock, in the sex with the higher white-matter burden. This is a substantial explanatory bonus and the submission collects one sentence of it.

And it changes what exogenous ketones are for. If the brain makes its own ketones by eating myelin, then supplying ketones from outside is not merely offering a substitute fuel. It is

removing the demand that drives the catabolism — a myelin-sparing intervention rather than an energetic one. That is a different mechanism, a different endpoint, and a different trial design: the readout is white-matter integrity on diffusion imaging, not cognition, and the population is peri-menopausal women, not patients with mild cognitive impairment.

We flag the discount plainly. This is a rodent result from a single programme, and the inference to human myelin is not yet supported by direct measurement of myelin lipid turnover across the human transition. Human myelin water imaging and lipidomic markers of myelin breakdown exist and could be applied to the peri-menopausal window. They have not been.

Grade: established in the ageing female rodent brain that myelin catabolism supplies ketogenic fuel, with plasma-brain ketone dissociation as the discriminating evidence. **Grade: unsupported** for the extension to human white-matter change across the menopause, which is plausible, important and untested.

18. The Plateau, and the Prediction It Makes

Eckert's Stage II is the part of the model that has been least noticed and that makes the sharpest prediction. It describes an interval in the early post-menopause as

> *"a new metabolic equilibrium in which the brain bioenergetics is decreased but still sufficient to maintain a quasi-normal activity."*

She equates this with the prodrome or with mild cognitive impairment. We think the equation with mild cognitive impairment is a mistake and the description of the state is important. Mild cognitive impairment is by definition a state of measurable cognitive deficit. A stable equilibrium sufficient for quasi-normal activity is by definition a state without one. These cannot both be Stage II, and the interesting one is the second: **a brain that is running on less and getting away with it.**

If that state exists, it has a signature, and the signature is a dissociation between two measurements that are usually assumed to move together. Metabolic capacity is down; performance is normal. The plateau is not the absence of pathology; it is the presence of successful compensation.

The prediction this makes about clinical trials is not subtle, and it has consequences we develop in Part V. During Stage II, cognition does not change — that is what "stable" means. A trial that enrols women in the early post-menopause and follows verbal memory for four or five years is measuring, by the theory's own account, a variable that the theory says will be flat in both arms. Such a trial can only be negative. Its negativity is not evidence against the theory; it is a prediction of the theory. To test the theory one must measure the metabolic quantity that is actually being defended: cerebral glucose utilisation, the substrate the brain has switched to, and the margin between demand and supply.

The human evidence for the plateau arrived one year after the submission, and it is remarkable. A multimodality neuroimaging study of the menopause transition — structure, connectivity, energy metabolism and amyloid — reported that the effects it found were specific to menopausal rather than chronological ageing, as established by comparison with age-matched men, and then reported this:

> *Brain biomarkers "largely stabilized post-menopause, and gray matter volume recovered in key brain regions for cognitive aging. Notably, GMV recovery and in vivo brain mitochondria ATP production correlated with preservation of cognitive performance post-menopause, suggesting adaptive compensatory processes."*

Stabilisation after the transition. Recovery of grey matter. ATP production correlating with preserved cognition. That is Stage II, imaged in living women, described by its authors in the language of compensation, and published after Eckert predicted it in a figure.

We are careful about what this shows. It is cross-sectional across stages rather than longitudinal within women, so "recovery" is inferred from a group difference rather than observed in an individual. The sample is a research cohort of midlife volunteers and not a population sample. And correlation between ATP production and cognitive performance is consistent with compensation and also with the simpler reading that people with better mitochondria think better. But the finding is in the right direction, at the right time, in the right sex, with the right control group, and it is the single strongest post-submission vindication of the framework.

The same study reported the other half of the picture: amyloid deposition was more pronounced in peri- and post-menopausal women carrying *APOE* ε4 than in genotype-matched men. The compensation succeeds in most and fails in a genetically identifiable subgroup — which is where the theory's two branches connect to the field's best-established risk allele, and which we take up in §25.

Grade: supported for the existence of a post-menopausal metabolic plateau with preserved cognition, resting on cross-sectional multimodality imaging in one cohort. **Grade: unsupported**, and probably mistaken, for the identification of that plateau with mild cognitive impairment. **Grade: established** that the metabolic changes of the transition are endocrine rather than chronological, given age-matched male comparison in three independent samples.

Part V — The Therapy and the Trial Record

19. What the Framework Predicts About Hormone Therapy

The submission's therapeutic core is a specific recommendation, and it is worth restating exactly because it is more precise than most theoretical papers manage:

> *"As a preventive strategy against AD, we propose that perimenopausal women (with irregular menstrual cycles) are treated with HRT consisting in estradiol administration, complemented with cyclic progesterone."*

Four separable predictions are packed into that sentence, and each can be tested independently.

Prediction 1 — the progestogen matters. Medroxyprogesterone acetate antagonises oestrogen-induced neuroprotection, while progesterone and 19-norprogesterone synergise with it. Therefore combined therapy using the synthetic progestin should perform worse than oestrogen alone, and should perform worse than oestrogen with natural progesterone.

Prediction 2 — the schedule matters. Continuous progesterone antagonises oestrogen's protective effect; cyclic administration, following the natural pattern, does not. Therefore cyclic regimens should outperform continuous ones.

Prediction 3 — the window matters. Prolonged oestradiol depletion downregulates oestrogen receptor expression, so treatment initiated late meets a brain that can no longer respond. Therefore early initiation should work and late initiation should not.

Prediction 4 — the target population is peri-menopausal, not post-menopausal. The intervention is meant to prevent the metabolic collapse, not to reverse it. Once the bioenergetic equilibrium is compromised, "the treatment may be inefficient in preserving neuronal integrity."

This is a falsifiable therapeutic programme. It has now been tested, in several designs, at large scale, and the results are neither the vindication its author expected nor the refutation its critics assume.

20. The Trial Record, in Order

The trial that created the problem. The Women's Health Initiative Memory Study randomised 4,532 postmenopausal women aged 65 or older and free of probable dementia to conjugated equine oestrogen 0.625 mg with medroxyprogesterone acetate 2.5 mg daily, or to placebo. Over a mean of 4.05 years, 61 women were diagnosed with probable dementia: 40 in the hormone arm against 21 on placebo. The hazard ratio was 2.05 (95% CI 1.21–3.48; 45 against 22 cases per 10,000 person-years; $P = .01$), an excess of about 23 cases per 10,000 women per year. Alzheimer's disease was the commonest classification in both arms. Mild cognitive impairment did not differ (HR 1.07, 95% CI 0.74–1.55).

Every element of that trial is what Eckert's framework says should fail: a synthetic conjugated oestrogen rather than oestradiol; medroxyprogesterone acetate, the specific progestin shown to antagonise neuroprotection; continuous rather than cyclic administration; and a population a decade and a half past the window. The submission says exactly this, and it is right.

A correction of record. The submission attributes this finding to a 2004 *JAMA* paper on conjugated equine oestrogen in women with hysterectomy at 291:1701. That is the main outcomes paper of the Women's Health Initiative's oestrogen-*alone* arm — a different trial arm, reporting cardiovascular and cancer endpoints rather than dementia. The result described belongs to the 2003 oestrogen-plus-progestin dementia paper. The description of the finding is accurate; the pointer is to the wrong trial. The submission also gives the participants' age as "over 68 years"; the enrolment criterion was 65 or older.

The observational record, which supports the framework. In the population-based Cache County Study, 1,768 women with detailed histories of age at menopause and hormone use were followed from 1995, with 176 incident Alzheimer's cases. Women who used any hormone therapy within five years of menopause had 30 per cent less risk of Alzheimer's disease (95% CI 0.49–0.99), especially with ten or more years of use. Risk was not reduced among women who began five or more years after menopause. And among those who began opposed oestrogen-progestin compounds in the three years before baseline, the adjusted hazard ratio was 1.93 (95% CI 0.94–3.96) — which the authors note is close to the 2.05 of the randomised trial.

The meta-analytic picture is the same shape. Across 45 observational reports covering 768,866 cases and 5.5 million controls, hormone therapy was associated with reduced Alzheimer's risk (RR 0.78, 95% CI 0.64–0.95) and reduced all-cause dementia (0.81, 0.70–0.94); the protection was carried by oestrogen-only therapy (0.86, 0.77–0.95) and absent for oestrogen-plus-progestogen (0.91, 0.775–1.069, not significant); and **midlife oestrogen-only therapy carried a 32 per**

cent reduction (0.685, 0.513–0.915). Across the six randomised reports in women aged 65 and over — 21,065 treated against 20,997 on placebo — the pooled relative risk of dementia was 1.38 (1.16–1.64), driven by combined therapy at 1.64 (1.20–2.25), with oestrogen-only not significant at 1.19 (0.92–1.54).

Predictions 1, 3 and 4 are therefore supported observationally, and prediction 1 is supported in randomised data. The progestogen does matter; the window does matter; late initiation is harmful.

The randomised test of the window, which was null. The Early versus Late Intervention Trial with Estradiol was designed to test exactly the timing hypothesis. Healthy women within six years of menopause or ten or more years after it were randomised to oral 17β-oestradiol 1 mg daily or placebo, with cyclic micronised progesterone gel for those with a uterus — a regimen that satisfies predictions 1, 2 and 3 as stated. Five hundred and sixty-seven women were analysed after a mean of 57 months. The estradiol-minus-placebo difference in verbal episodic memory was −0.06 (95% CI −0.22 to 0.09; $p = 0.33$). The interaction between treatment and proximity to menopause — the timing hypothesis itself — had a p value of **0.88**. Nothing differed for executive function or global cognition.

The parallel Kronos Early Estrogen Prevention Study randomised 727 recently postmenopausal women to oral conjugated equine oestrogen 0.45 mg, transdermal estradiol 50 μg, or placebo, all active arms with cyclic micronised progesterone for twelve days a month, for four years, and found no cognitive benefit or harm. Its observational continuation recontacted participants about ten years after the trial ended; of 622 invited, 299 returned, with cognitive data available across both phases for 275. Treatment allocation did not modify cognitive trajectory at any point. The authors' conclusion is careful and worth reproducing: the results "provide reassurance about the long-term neurocognitive safety of mHT for symptom management in healthy, recently postmenopausal women, while also suggesting that mHT does not improve or preserve cognitive function in this population."

The register studies, which disagree with each other. Two large national database analyses reached opposite conclusions on the same question. In the UK, 118,501 women aged 55 and over with a dementia diagnosis were matched to 497,416 controls; overall there was no increased risk with hormone therapy, a *decreased* global risk among those under 80 taking oestrogen-only therapy for ten years or more (adjusted OR 0.85, 95% CI 0.76–0.94), and increased Alzheimer's risk with oestrogen-progestogen for five to nine years (1.11, 1.04–1.20) and ten or more years (1.19, 1.06–1.33). In Denmark, 5,589 incident dementia cases from a population of women aged 50 to 60 in 2000 were matched to 55,890 controls; oestrogen-progestogen therapy carried a hazard ratio of 1.24 (1.17–1.33) for all-cause dementia, with a clear duration–response from 1.21 at one year or less to 1.74 (1.45–2.10) beyond twelve years, and — the finding that matters most here — the association **persisted among women treated at 55 or younger** (1.24, 1.11–1.40).

That last result is the sharpest challenge to prediction 3 in the literature. It says the harm of combined therapy is not confined to late initiation. Confounding by indication is a real and unresolved objection — women prescribed hormone therapy differ from those who are not, in ways registers capture poorly — but the duration–response gradient is not easily produced by confounding, and the theory has no ready answer.

The pathology endpoint, which restores part of the picture. One study has asked the timing question with a biological rather than a cognitive readout. In 292 cognitively unimpaired participants — 193 women, 99 men, mean age 67 — imaged for both tau and amyloid, female sex, earlier age at menopause and hormone therapy use were each associated with higher regional tau in those with elevated amyloid, across medial and lateral temporal and occipital regions. Within the hormone users, **late initiation — more than five years after menopause — was associated with higher tau than early initiation** ($P = .001$).

Two of those results are what the framework predicts and one is not. Earlier menopause predicts more tau: predicted. Late initiation predicts more tau than early: predicted. Hormone therapy use overall predicts more tau: not predicted, and the obvious candidate explanation is that women who take hormone therapy are women with more severe vasomotor symptoms, which are themselves associated with worse markers. The study is cross-sectional and observational and its authors say so. But it is the only place in the literature where the timing hypothesis has been examined against pathology rather than performance, and where it is examined that way, it survives.

21. Why the Trials Cannot Adjudicate the Theory, and What Would

We now put the two halves of the record together, because the pattern is not random and the theory has a defence.

Endpoint	Design	Result	Direction for the theory
Dementia incidence, age 65+	Randomised, combined therapy	HR 2.05	Predicted
Dementia incidence, pooled RCTs 65+	Meta-analysis	RR 1.38; combined 1.64; oestrogen-only ns	Predicted
Alzheimer's incidence, midlife oestrogen-only	Meta-analysis of observational	RR 0.685	Predicted
Alzheimer's incidence, use within 5 y of menopause	Population cohort	30% reduction	Predicted
Verbal memory, early vs late initiation	Randomised, 5 y	No effect; interaction $p = 0.88$	Contrary
Cognition, early postmenopause	Randomised, 4 y, and 10 y follow-up	No effect	Contrary
Dementia, combined therapy at ≤55	National register	HR 1.24, duration–response	Contrary
Regional tau at elevated amyloid	Cross-sectional PET	Earlier menopause and late initiation → more tau	Predicted

Read down the table and a rule emerges. **Where the endpoint is disease incidence or pathology, the predictions hold. Where the endpoint is cognitive performance in the years immediately after menopause, they fail.**

This is where Eckert's Stage II earns its keep, and it is a defence about measurement rather than about effect. Her own model says that the early post-menopausal years are a *stable* interval — reduced bioenergetic throughput, preserved function. If that is true, then cognition in healthy women in the first five years after menopause is a variable with almost no signal in it: it does not decline in the placebo arm, so there is nothing for the treatment arm to prevent. A five-year trial of

verbal memory in that population is powered to detect a change that the theory predicts will not occur in either group.

The endpoints the theory actually specifies are metabolic, and they have never been primary outcomes of a hormone trial:

1. **Cerebral metabolic rate of glucose**, regionally, by FDG-PET — the quantity the hormone is supposed to defend.
2. **The substrate the brain has switched to** — cerebral acetoacetate or β-hydroxybutyrate metabolism, and the ratio of ketone to glucose utilisation, which is the direct measure of whether the switch is occurring.
3. **White-matter integrity** — which, on the myelin-catabolism mechanism of §17, is what the switch costs.

A trial with those endpoints, in peri-menopausal women, over three years, would test this theory. No such trial has been run. This is not a rhetorical escape hatch: it is a specific, feasible, pre-registrable design, and the failure to run it is the reason a twenty-year-old hypothesis remains unadjudicated.

We are also obliged to state the version of events in which the theory is simply wrong. The observational-versus-randomised divergence in the hormone literature has a standard and unglamorous explanation: healthy-user bias. Women who take hormone therapy in midlife are wealthier, healthier, better educated and better engaged with medical care, and every one of those is a dementia risk factor in its own right. That single mechanism produces the entire pattern of "protective in cohorts, null in trials" without any brain biology at all. The timing hypothesis and healthy-user bias make nearly identical predictions across the existing evidence base, and the existing evidence base cannot separate them. The metabolic endpoints above can, because healthy-user bias does not predict a change in cerebral glucose utilisation on the treatment arm of a randomised trial.

Grade: established that combined therapy with medroxyprogesterone acetate initiated after 65 increases dementia risk. **Grade: established** that randomised hormone therapy in early postmenopause has no effect on cognition over four to ten years. **Grade: supported** that oestrogen-only therapy initiated near the menopause is associated with reduced Alzheimer's risk in observational data, with healthy-user bias unexcluded. **Grade: supported** that late initiation is associated with higher tau burden than early initiation. **Grade: unsupported** — untested rather than refuted — that hormone therapy initiated at the peri-menopause preserves cerebral glucose metabolism.

22. The Rest of the Menu, Graded

The submission proposes four interventions. It presents them in a hierarchy — hormone therapy as the logical primary strategy, diet and exercise as general support, mitochondrial boosters as adjuncts, and alternative brain fuel as the fallback for women whose transition is already advanced. Set against the randomised record, that hierarchy is close to exactly inverted.

Diet. The Mediterranean and Okinawan patterns are argued for on epidemiological and mechanistic grounds. The randomised test of the most Alzheimer-targeted version of that pattern — a three-year, two-site trial in 604 cognitively unimpaired older adults with a family history of dementia — found improvement in global cognition in both arms and no significant difference between them: 0.205 against 0.170 standardised units, mean difference 0.035 (95% CI −0.022 to 0.092, $P = 0.23$), with white-matter hyperintensities, hippocampal volume and total grey and white matter also similar. **Grade: unsupported** as a cognitive intervention on randomised evidence; the observational association is real and the causal claim is not.

Exercise. The mechanistic case is good: exercise increases mitochondrial biogenesis, oxidative phosphorylation and antioxidant defences in brain. The clinical case in established disease is poor. In 494 people with mild to moderate dementia randomised 2:1 to a four-month supervised aerobic and strength programme or usual care, fitness improved and the ADAS-cog at twelve months was *worse* in the exercise arm: adjusted between-group difference −1.4 (95% CI −2.6 to −0.2, $P = 0.03$), a small difference of uncertain clinical meaning but not in the hoped-for direction. **Grade: unsupported** as a treatment for established dementia. Its standing as midlife prevention is a separate question with better prospects and no adequate randomised test.

Multidomain intervention. The best evidence in this territory is for the combination rather than any component. In 1,260 at-risk adults aged 60 to 77 randomised to two years of diet, exercise, cognitive training and vascular risk monitoring or to general health advice, the between-group difference in neuropsychological test battery change was 0.022 per year (95% CI 0.002–0.042, $p = 0.030$). Positive, replicated in design across several countries, and small. **Grade: supported.**

Ginkgo biloba extract. The submission gives it a paragraph and cites mitochondrial mechanism plus positive findings in subjective memory impairment and mild cognitive impairment. It does not cite either of the two large prevention trials. In 3,069 community volunteers aged 75 or older followed a median of 6.1 years, 120 mg twice daily gave a hazard ratio for all-cause dementia of 1.12 (95% CI 0.94–1.33, $P = .21$) and for Alzheimer's disease 1.16 (0.97–1.39, $P = .11$) — numerically adverse, statistically null. In 2,854 adults aged 70 or older with memory complaints followed five years, the hazard ratio for conversion to probable Alzheimer's disease was 0.84

(0.60–1.18, p = 0.306). **Grade: unsupported** for dementia prevention, on two adequately powered negative trials that the submission does not mention. The omission matters more than the others in this section, because these trials tested precisely the proposition being advanced.

Neurosteroids. Allopregnanolone is described as "currently undergoing clinical trials for the treatment of AD." Six years later, the published clinical work remains a phase 1b/2a multiple-ascending-dose study in 24 participants — 18 on drug, 6 on placebo — over twelve weeks, with exploratory imaging outcomes. The compound remains biologically interesting and clinically unproven, and the gap between the mechanistic literature and the clinical evidence has not narrowed. **Grade: unsupported**, in the sense of untested at adequate scale.

Alternative fuel. This is the intervention the submission places last, and the evidence for it is the best in the list. The rationale is established: in mild Alzheimer's dementia, glucose metabolism is reduced by about 13 per cent while acetoacetate metabolism is statistically normal. The clinical test exists: in a six-month randomised trial in mild cognitive impairment, a ketogenic medium-chain triglyceride drink at 15 g twice daily against placebo improved free and cued recall (P = .047), category fluency (P = .024), naming (P = .033) and Trail-Making errors (P = .017), with outcomes correlating with achieved plasma ketone levels — a dose–response relation that is difficult to obtain by chance and is the strongest feature of the result. The effects are modest, the trial is small (39 against 44), and it is a cognitive endpoint in a population selected for having a deficit to improve. **Grade: supported**, and the best-evidenced item on the list.

The inversion is worth stating plainly, because it is the most actionable conclusion in this evaluation. **The intervention Eckert argues for at greatest length has the worst randomised record. The intervention she offers as a fallback for women who have missed the window has the best.** If the theory is right that the disease is a failure to switch fuels, then supplying the fuel is the intervention that acts on the mechanism most directly, does not require the hormone receptor system to still be responsive, does not carry oncological or thrombotic liability, and is not confined to women.

23. The Direction the Programme Has Actually Taken

Since 2020 the laboratory has pursued the therapeutic proposition, and the direction it has taken amounts to a tacit acceptance of the trial record.

A different oestrogen. Estetrol is a fetal oestrogen with a selective receptor profile and a more favourable thrombotic and oncological safety margin than 17β-oestradiol. Tested against amyloid and tauopathy cell models, it raised ATP levels, mitochondrial membrane potential and oxidative respiration in all models — outperforming 17β-oestradiol in the P301L tau line — and promoted neurite outgrowth, with effects mediated through ERα, ERβ and GPER1 and accompanied by upregulation of the mitochondrial phosphate carrier *SLC25A23* and downregulation of the complex I subunit *NDUFA1*.

This is the framework's central proposition being pursued with the liability engineered out. It is also, we note, a cell-model result, and the history of this field is a history of steroids that worked in cells.

A different route to the same organelle. Mitochondrial transplantation — isolating intact mitochondria from astrocytic cells and introducing them into tau-expressing neurons — raised bioenergetics and restored neurite outgrowth. As therapy this is remote. As an experiment it is the cleanest available test of whether the bioenergetic deficit is *sufficient* for the cellular phenotype, and the answer it gives is yes.

Quality control rather than capacity. Work on spermidine, on translocator-protein ligands acting through p62, and on dietary mitophagy enhancers reflects a shift of emphasis from how much ATP the cell can make to how well it disposes of the machinery that has stopped making it. That is the right shift. A cell with a frozen fission-fusion network and impaired mitophagy — which is what the tau cell models show — cannot benefit from a booster, because it cannot clear what is broken.

What the programme has not done, and what the framework most needs, is to move any of this into the window the theory identifies. Every one of these results is in a cell model of established proteinopathy. The theory's claim is about a metabolic transition in cognitively normal women in their late forties. The distance between the two is the distance the work still has to travel.

Part VI — What the Argument Cannot Carry

24. The Male Half of the Disease, and the Test Nobody Ran

A theory that explains Alzheimer's disease by the withdrawal of ovarian steroids owes an account of the third of cases that occur in people who never had ovaries. The submission's only remark on the subject is that testosterone also raises mitochondrial bioenergetics, that the mechanisms are unclear, and that the topic has received little attention. That is a description of a gap, not a theory of one.

The gap matters more than it looks, because on the framework's own logic the male case should behave differently in a specific and checkable way. **Male gonadal steroid decline is a slope; female decline is a step.** A gradual fall over four decades gives the brain time to adjust its substrate economy incrementally, and never presents it with the acute demand that Stage I is a response to. The framework therefore predicts, without needing to be extended, that men should show a slower, shallower version of the same metabolic drift and no discrete failure point — which is consistent with the biomarker studies in which men showed no abnormality relative to age-matched women, and inconsistent with the fact that men develop about a third of the disease. If the mechanism is a step, and men have no step, then either men reach the same endpoint by a different mechanism, or the step is not the mechanism.

The theory has a way of resolving this, and it involves a fact the submission does not use. **Oestradiol in the male brain is made in the male brain.** Aromatase, the product of *CYP19A1*, converts testosterone to oestradiol locally, and is expressed in human basal forebrain, cerebral cortex, hippocampus, thalamus, cerebellum and brainstem, in neurons and in a subpopulation of astrocytes, well outside the classical reproductive areas. Male brain oestradiol is therefore a function of circulating androgen. Withdrawing androgen from a man withdraws oestradiol from his brain.

This converts a limitation into a prediction, and the prediction has a natural experiment attached to it that has been running for thirty years.

Androgen deprivation therapy for prostate cancer is the male oophorectomy. It is an abrupt, near-total, iatrogenic withdrawal of gonadal steroid, administered to a large, well-documented, elderly male population, with dose and duration recorded in claims data. If the mechanism of the female theory is steroid withdrawal acting on brain bioenergetics, men receiving androgen deprivation should show the female pattern.

They do, modestly and consistently.

In a Surveillance, Epidemiology and End Results–Medicare cohort of 154,089 men newly diagnosed with prostate cancer, of whom 62,330 received androgen deprivation within two years, followed for a mean of 8.3 years, Alzheimer's disease occurred in 13.1 per cent of exposed against 9.4 per cent of unexposed (HR 1.14, 95% CI 1.10–1.18) and dementia in 21.6 against 15.8 per cent (HR 1.20, 95% CI 1.17–1.24), with a dose gradient across categories of exposure and a number needed to harm of 18 for Alzheimer's disease and 10 for dementia. An earlier electronic-record study using propensity matching in 16,888 men found a hazard ratio of 1.88 (95% CI 1.10–3.20) with a significant duration effect. A systematic review pooling 28 studies and more than 2.5 million patients reported hazard ratios of 1.20 (1.11–1.29) for dementia and 1.26 (1.10–1.43) for Alzheimer's disease, with vascular dementia not significantly raised at 1.30 (0.97–1.73).

Three things about this literature deserve saying.

It is the right shape. Abrupt steroid withdrawal, in either sex, is associated with a 15 to 25 per cent excess of dementia, with a dose gradient. The effect sizes in men (1.14–1.26) and in women after early oophorectomy (1.46) are of the same order, with the female effect larger — which is what one would expect if the female withdrawal is more complete and occurs at a younger brain age.

It is not clean. Men receiving androgen deprivation have more advanced cancer, more comorbidity, more treatment contact and therefore more diagnostic opportunity. Confounding by indication and by surveillance intensity is unresolved, and the effect sizes are in the range where residual confounding is a live explanation. The literature is not unanimous; individual cohorts have reported null results, and the pooled estimate carries substantial heterogeneity.

And the specificity finding cuts against a general-frailty explanation. In the pooled analysis, androgen deprivation was associated with dementia at 1.20 and with Alzheimer's disease at 1.26 — but the association with vascular dementia was not significant. A confounding-by-frailty account predicts a broad excess across dementia subtypes and particularly across the vascular ones, since androgen deprivation carries known cardiometabolic liability. A steroid-withdrawal account predicts the degenerative subtype. The data favour the second, weakly.

We regard this as the most important extension the framework could make and has not made. It would give the theory a male arm, tested in humans, at population scale, with a dose gradient, in data that already exist. The specific prediction to test is sharper than anything currently in the literature: **if the mechanism is bioenergetic, men on androgen deprivation should show the female metabolic signature — regional hypometabolism in Alzheimer-vulnerable cortex, and evidence of substrate switching — within one to two years of starting treatment, and it should be absent in matched men with prostate cancer not receiving it.** That is a small imaging study, it is feasible today, and it would either give this theory a second sex or take it away.

Grade: established that abrupt androgen withdrawal in men is associated with a modest excess of dementia and Alzheimer's disease, with dose gradient, in large cohorts and a pooled analysis, with residual confounding unexcluded. **Grade: unsupported** — untested — that androgen deprivation produces the bioenergetic signature the framework predicts. **Grade: unsupported** for the submission's implicit position that the male path is a matter for future work rather than a test of the present theory.

25. Genetics: Where the Theory Gains and Where It Frays

The submission's treatment of genetics occupies two sentences: that women carrying an *APOE* ε4 allele develop the disease earlier than male carriers, and a citation. The underlying result is more interesting than the summary, and it is better for the theory than the summary suggests.

In a meta-analysis pooling 27 studies and nearly 58,000 participants, ε3/ε4 carriers of both sexes had closely similar overall Alzheimer's risk between ages 55 and 85: odds ratio 3.09 (95% CI 2.79–3.42) in men, 3.31 (3.03–3.61) in women, with no significant difference. **The difference appears in a window.** Between 65 and 75, women carriers had an odds ratio of 4.37 (3.82–5.00) against 3.14 (2.68–3.67) in men, $P = .002$. For mild cognitive impairment, the same pattern: no sex difference across the full age range, but a female excess between 55 and 70. And the protective ε2 allele protected women more than men — 0.51 (0.43–0.61) against 0.71 (0.60–0.85), $P = .01$.

A window is exactly what an endocrine theory should predict, and it is a much stronger result for Eckert than a main effect would have been. A permanent female excess in ε4 risk would suggest a constitutive sex difference — chromosomal, developmental, or lifelong. A transient excess confined to a fifteen-year band suggests a time-limited exposure that interacts with the genotype. The submission has the result and states it as "earlier," which loses the shape.

The window's position is, however, awkward for the simplest version of the timing claim. It opens at about 65, which is roughly fourteen years after median menopause, and closes at 75. If the endocrine transition were interacting with ε4 to accelerate disease, the naive expectation is divergence closer to the exposure. The reading that fits is that the interaction acts on *conversion* — the transition from a compensated to a decompensated state — rather than on initiation, which is again the branch-point model rather than the entry-door model.

The imaging evidence points the same way. In the multimodality study of the menopause transition, amyloid deposition was more pronounced specifically in peri- and post-menopausal women carrying ε4, relative to genotype-matched men. In the earlier cross-sectional staging study, amyloid was exacerbated in ε4-positive post-menopausal women relative to all other groups. The transition does not raise amyloid in everyone. It raises it in carriers.

That is a compensation-failure signature: a universal stressor, a genetically determined reserve, and decompensation concentrated where the reserve is lowest. It is also, we note, the point at which

this theory makes contact with the mainstream genetics of the disease, which the submission otherwise leaves untouched. There is no discussion of *APP*, *PSEN1* or *PSEN2*, of trisomy 21, or of the more than seventy risk loci from genome-wide association. A theory of sporadic late-onset disease is not obliged to explain autosomal dominant disease, but it is obliged to say why not, and this one does not.

Grade: established that the *APOE* ε4 excess in women is confined to an age window rather than being a general effect. **Grade: supported** that the menopause transition raises amyloid burden preferentially in ε4 carriers. **Grade: unsupported** for any account of how this framework relates to the monogenic forms of the disease, which is a silence rather than an error.

26. The Unnamed Predecessor

In 2004 a mitochondrial cascade hypothesis for sporadic Alzheimer's disease was published. Its core assumptions were that a person's genes determine baseline mitochondrial function and durability; that this durability determines how mitochondria change with age; and that critical changes in mitochondrial function initiate the other pathologies characteristic of the disease — with amyloid generation cast as a downstream "reset response" to elevated reactive oxygen species rather than as an initiating event. A 2010 restatement added the maternal-inheritance endophenotype evidence and the prediction, then still contrarian, that amyloid-directed therapies would have at best very limited clinical benefit.

That is the cascade Eckert's submission describes. Baseline mitochondrial capacity set by inheritance; age-related decline; radical production rising; amyloid and tau downstream; a vicious cycle closing. The overlap is not partial. It is the same hypothesis.

The hypothesis is not cited. The bibliography contains 107 references; it includes a ketogenic-diet feasibility study on which the hypothesis's author is a co-author, and no statement of the hypothesis itself.

We do not read this as misconduct — the mitochondrial-cascade framing has diffused widely enough that many authors now restate it as background — but it has two costs, and both are analytical.

It misplaces the novelty. The submission's genuinely new contribution is not the cascade. It is the *trigger*: the identification of a dated, universal, sex-specific event that supplies the increment which pushes a declining system past its margin. That is a real addition to a sixteen-year-old framework, and stating it as an addition would have made it sharper. Instead the paper presents an established hypothesis and its own extension as a single new theory, which makes the whole thing look more speculative than the extension alone would.

It loses a test, and the test has already returned an answer. The predecessor hypothesis makes a prediction the submission would have benefited from: that risk should track the maternal line, because mitochondrial DNA is maternally inherited.

It does. Among 49 cognitively normal adults aged 50 to 80, those with a *maternal* family history of late-onset Alzheimer's disease showed reductions in cerebral glucose metabolism in the same regions as clinically affected patients — posterior cingulate and precuneus, parietotemporal and frontal cortex — relative both to those with no family history and to those with a *paternal* history,

with the groups comparable on demographic and neuropsychological measures. The mechanism was then measured directly and peripherally: in 36 cognitively normal individuals aged 27 to 71, platelet mitochondrial cytochrome oxidase activity, corrected for citrate synthase, was reduced by 29 per cent in those with a maternal history relative to those with no family history and by 30 per cent relative to those with a paternal history.

Two things about that second result matter here. It is **complex IV** — the same complex that Eckert's own mouse work assigns to the amyloid limb, and the same enzyme that is reduced by 25 to 30 per cent in Alzheimer's cortex at autopsy. And it is measured in **platelets**, the identical peripheral assay used in the perimenopausal staging study, which means the two literatures are reporting the same measurement in the same units and have never been put side by side.

The synthesis is available and nobody has made it: **baseline complex IV capacity is inherited down the maternal line, and the menopause is the event that tests it.** A woman inherits her margin from her mother and is examined on it at 51. That is the theory this framework should be stating, and the submission does not raise the maternal-inheritance literature at all.

Grade: established that the mitochondrial cascade framing predates the submission by sixteen years. **Grade: supported** that the submission's distinctive contribution is the trigger rather than the cascade.

27. The Over-Prediction Problem

Stated as an entry-door theory, this framework over-predicts by a factor of four or five, and the arithmetic is straightforward.

Essentially every woman who survives to sixty undergoes the menopause. The lifetime risk of dementia or Alzheimer's disease for a woman at age 45, accounting for competing mortality, is about one in five. If the menopause opens the door, four in five women walk up to an open door and do not go through it.

There are three ways to respond to this, and only one of them is honest.

The first is to say that the exposure is necessary but not sufficient, and that other factors determine who progresses. This is true and it is nearly empty: it converts the theory into the claim that a universal event is one of many contributors, which is compatible with almost any evidence and predicts almost nothing.

The second is to argue that subclinical versions of the process occur in the other four-fifths — that all post-menopausal women have some degree of the lesion and only some cross the clinical threshold. This is more defensible, and the biomarker data support a version of it: hypometabolism and increased amyloid are found in peri- and post-menopausal women as a group, not only in those who will decline. But it needs a threshold model, and the submission does not supply one. Without a stated threshold, "everyone has it subclinically" is unfalsifiable.

The third is the branch-point reading, and it is the one the evidence supports: **the exposure is universal, the outcome is determined by the adequacy of the compensatory response, and the compensation succeeds in most women.** On this reading the four-fifths are not an embarrassment. They are the phenomenon — the successful branch, the thing that needs explaining and, if it can be explained, imitated.

We note that the same arithmetic applies to the theory's therapeutic programme and sharpens it usefully. If four in five exposed women do not develop the disease, then a preventive intervention applied to all peri-menopausal women is treating five to prevent one, with the risk profile of hormone therapy applied to all five. That is a poor bargain, and it is the real argument against population-wide hormonal prevention regardless of whether the mechanism is correct. It is also the argument for the fuel strategy, whose risk profile is very different, and for stratification: the framework's practical value lies in identifying *which* women are failing the switch, which is a measurement problem, not a treatment problem.

Grade: unsupported for the theory stated as sufficient causation. **Grade: supported** for the theory stated as a universal exposure with variable compensation.

28. The Circularity That Has to Be Watched

There is a methodological trap at the centre of this literature, and it is worth naming because the theory has walked close to it and, on balance, walked past it.

Reduced cerebral glucose metabolism is used in this framework in two roles. It is the **proposed mechanism** of the disease — the bioenergetic failure that kills neurons. And it is, in the imaging studies that supply the human evidence, a **defining feature of the "Alzheimer's endophenotype"** whose emergence across the menopause is being demonstrated.

If hypometabolism defines the endophenotype, then demonstrating that menopause produces hypometabolism demonstrates that menopause produces the endophenotype by definition. What it does not demonstrate is that menopause produces Alzheimer's disease, because the inference from the endophenotype to the disease is the thing at issue. A finding that a physiological transition reduces brain glucose uptake is a finding about brain glucose uptake. Pregnancy, hypothyroidism, sleep deprivation, anaesthesia and depression all reduce cerebral metabolic rate, and none of them is Alzheimer's disease.

The escape from the circle requires a marker that is not metabolic, and the studies in this literature have one — in fact two. The same participants were imaged for amyloid and, in the later work, for tau. Amyloid deposition was higher in peri- and post-menopausal women than in pre-menopausal women and than in age-matched men, and higher again in ε4 carriers. Regional tau was higher in women than in men at a given amyloid burden, and higher in women with earlier menopause. Those are proteinopathy findings, independent of the metabolic definition, and they are what makes the endocrine literature evidence about Alzheimer's disease rather than evidence about brain energy.

The circle is therefore escapable and has been escaped, but only in the studies that measured amyloid and tau. Any future work in this area that rests on FDG-PET alone will re-enter it. We flag it because the submission's proposed clinical protocol — its final figure — stages women by menstrual status and assigns FDG-PET as the diagnostic investigation, without a proteinopathy marker. As a research design that protocol cannot distinguish the disease from the transition.

Grade: established that the transition affects amyloid and tau markers and not only metabolic ones, which is what licenses the disease claim. **Grade: unsupported** for the proposed FDG-PET-only staging protocol as a means of identifying women on a disease trajectory rather

than women who have been through the menopause.

Part VII — What the Programme Adds, and What Would Settle It

29. Five Additions, and One Left on the Bench

Having graded the argument, we can state what it contributes. We are trying to be exact rather than generous: several claims commonly attributed to this framework are not its own, and the ones that are its own are more specific than the summaries suggest.

First: a dissociation rather than an association. The literature is full of demonstrations that mitochondria are impaired in Alzheimer's disease. Very few of them say *which* lesion damages *which* component. This programme does: in a genetic background carrying both pathologies, deregulation of complex I was tau-dependent and deregulation of complex IV was amyloid-dependent, at the protein and at the activity level, with a synergistic loss of membrane potential appearing only in the double-pathology animals and only at eight months. This is the difference between a correlate and a mechanism. It also has an immediate consequence that nobody has drawn: if the two proteins damage different complexes, then respiratory-chain profiling is a candidate *molecular staging* method — a brain in which complex IV is disproportionately affected is, on this account, further along the amyloid limb than the tau limb, and vice versa.

Second: both arrows of the vicious cycle, demonstrated in mammals. Assertions of a mitochondrial vicious cycle in neurodegeneration are ubiquitous and usually rest on one direction. Here the forward arrow is established across mouse, cell and human tissue, and the return arrow — a primary genetic mitochondrial lesion producing more tau pathology and more neurodegeneration — is established in a mouse cross the same group took part in. Independent confirmation of the return arrow comes from a different system with a human epidemiological correlate: a natural complex I inhibitor produces tau redistribution and neuronal death, rescued by restoring NADH oxidation and not by antioxidants. A theory that requires a closed loop now has one.

Third: the only clock in late-onset Alzheimer's disease that can be read forwards. This is the contribution most worth having and the one least often stated in these terms. Every biomarker in the field dates the process by measuring what has already accumulated, which means the start of the process is unobservable in anyone not already under surveillance. The menopause is dated by the patient, without instrumentation, in half the population, at a median age near 51, and it precedes the median age of symptomatic disease by about the length of the estimated prodrome. Whether or not it initiates anything, it is a prospectively identifiable moment at which a large, defined, universal metabolic stress is applied. Nothing else in the disease has that property.

Fourth: the disease as a failed adaptation. The two-branch model — successful substrate switch and healthy ageing, or failed switch and collapse — relocates the explanandum from the exposure to the response. It converts a hormone-deficiency theory into a resilience theory with a named mechanism, a measurable readout and a dated window. It resolves the over-prediction problem that any universal-exposure theory faces. It makes the four-fifths who do not get the disease into the phenomenon rather than the residue. And in the year after the submission it was observed in living women: biomarkers stabilising after the transition, grey matter recovering, and in vivo brain ATP production correlating with preserved cognition, described by the observers as adaptive compensation.

Fifth: a staging protocol a clinician could use on Monday. The submission's final figure stages women by the simplest available clinical variable — regular cycles, irregular cycles, no cycles — and assigns each stage a different investigation and a different intervention. Almost no theoretical paper in this field produces anything of the kind. The specific assignments are, in our grading, partly wrong: the diagnostic arm rests on FDG-PET alone and therefore cannot distinguish disease trajectory from endocrine transition (§28), and the therapeutic arm leads with the intervention that has the worst randomised record and treats the best-evidenced one as a fallback (§22). But the *form* is right, and the form is the contribution: a theory of a dated exposure ought to produce a schedule, and this one does.

And one left on the bench. In the cell model that established the complex I lesion, overexpressing *wild-type* tau did not merely spare the respiratory chain — it improved mitochondrial function and dynamics and *raised* complex I activity, while the P301L mutant lowered both. Fourteen years later, that observation has not been followed up in neurons or in vivo, and it should be, because three important things turn on it.

If normal tau is a positive regulator of complex I, then **tauopathy is partly a deficiency state** and the deficit measured in disease is the sum of a toxic gain and a lost housekeeping function. **Mouse models built to reproduce the gain will systematically understate the human deficit**, which would help explain the persistent gap between the severity of mitochondrial phenotypes in patients and their mildness in models. And **any therapy that lowers total tau is titrating away a mitochondrial regulator** without measuring the thing it regulates. Antisense oligonucleotides and active immunotherapies against tau are now in human trials. None of them, to our knowledge, has a respiratory-chain endpoint. On this laboratory's own fourteen-year-old finding, they should.

3o. The Ledger

Twenty-four claims, graded as set out in §3. Claims are stated in the form the submission advances them, except where noted.

#	Claim	Grade	Basis
1	The brain is disproportionately dependent on mitochondrial oxidative phosphorylation running on glucose	Established	Physiology; fuel-flexibility constraints
2	Brain ageing involves falling antioxidant defence, rising oxidative damage and declining oxidative phosphorylation	Established	Human post-mortem, in vivo spectroscopy, CSF F2-isoprostane
3	Mutant tau produces a complex I deficit with reduced ATP and impaired mitochondrial dynamics	Established	Mouse and cell, cross-validated in human FTDP-17 tissue
4	Wild-type tau *raises* complex I activity and improves mitochondrial dynamics	Supported	One cell model, one laboratory, unreplicated in 14 years
5	Complex I deregulation is tau-dependent and complex IV deregulation amyloid-dependent	Established in mouse	iTRAQ across 1,275 proteins, protein and activity levels
6	That dissociation holds in human brain — complex IV limb	Supported	Cortical cytochrome oxidase reduced 25–30%
7	That dissociation holds in human brain — complex I limb	Unsupported	Cortical complex I largely spared; human lesion is in the TCA cycle
8	Amyloid and tau act synergistically on mitochondrial membrane potential	Established in mouse	Effect present only in triple transgenics at 8 months
9	A primary mitochondrial lesion increases tau pathology	Established	Harlequin × P301L cross; annonacin in primary neurons
10	The route from complex I failure to tau pathology is energetic, not oxidative	Established	Rescued by NDI1, not by antioxidants

#	Claim	Grade	Basis
11	Bioenergetic deficit precedes plaques, tangles and cognitive deficit	Supported	Mouse; and hypometabolism in *APOE* ε4 carriers aged 20–39
12	That deficit is *initiated* by the menopause	Unsupported	Present three decades earlier in ε4 carriers
13	Oestradiol regulates brain glucose transport, glycolysis, OxPhos and antioxidant defence	Established	Cell, rodent, ovariectomy-replacement
14	Endocrine and chronological brain-ageing programmes are separable	Established in rodent	Transcriptomic, FDG-PET, mitochondrial and LTP endpoints track cycle status
15	Peri- and post-menopausal women show hypometabolism, higher amyloid and lower regional volumes vs pre-menopausal women and age-matched men	Established	Three independent samples with male controls
16	Menopausal status outranks other measured hormonal, medical and lifestyle factors as a correlate	Established	Multivariable selection in 121 midlife adults
17	Women are two-thirds of Alzheimer's patients	Established (prevalence)	US and European prevalence data
18	That ratio demonstrates a female-specific biological mechanism	Unsupported	Cumulative incidence similar in Framingham; cited sources attribute it to survival
19	Oophorectomy before natural menopause raises dementia risk, more so the earlier it occurs	Established	HR 1.46, trend $p < 0.0001$; replicated in UK Biobank
20	Oestrogen to age 50 abolishes most of that excess	Supported	Non-randomised within-cohort comparison
21	The ageing female brain switches to alternative substrates; failure of the switch is the disease	Supported	Rodent; two-branch pattern in nonTg vs 3xTgAD
22	The alternative fuel is generated by catabolising myelin	Established in rodent	Brain ketones rise while plasma ketones fall
23	Combined hormone therapy begun after 65 increases dementia risk	Established	HR 2.05; pooled RCT RR 1.38
24	Hormone therapy begun at the peri-menopause prevents the metabolic collapse	Unsupported (untested)	Never tested against a metabolic endpoint

Nine established, eight supported, four unsupported as stated, and three — claims 7, 12 and 18 — contradicted by evidence that was available when the submission was written.

31. Five Conditions That Would Refute the Reformulated Theory

We restate the theory in the form we think the evidence supports:

> *The menopause is a scheduled, universal bioenergetic stress test, applied to half the population at a known date, whose outcome is determined by mitochondrial reserve the patient already had; Alzheimer's disease in women is what follows when the compensatory substrate switch fails.*

A theory worth having says what would kill it. Five things would.

1. A flat onset slope. If, among women who develop Alzheimer's disease, the age at symptomatic onset does not track the age at final menstrual period, the menopausal clock is a coincidence of medians and the timing claim is void. This is the cheapest and most decisive test available.

2. No metabolic signature in the male natural experiment. If men undergoing androgen deprivation do not develop the regional hypometabolic pattern and the substrate shift within one to two years, then steroid withdrawal is not what produces the bioenergetic lesion, and the female association is confounded.

3. Compensation without protection. If the women who show the strongest substrate switch — highest cerebral ketone utilisation, best-preserved ATP production — are not the women who go on to remain cognitively intact, then the switch is a marker rather than a mechanism and the branch-point model fails.

4. Fuel supplementation with no metabolic effect. If exogenous ketosis raises plasma and brain ketone levels in peri-menopausal women without altering the trajectory of cerebral glucose metabolism, white-matter integrity, or downstream pathology markers, then supplying the second fuel does not relieve the demand the theory says drives the lesion.

5. Reserve without inheritance. If baseline mitochondrial capacity — indexed peripherally by complex IV activity, or centrally by resting cerebral metabolic rate — does not predict who decompensates after the transition, then the theory has no account of why the same universal exposure produces such different outcomes, and reverts to the empty form criticised in §27.

32. Ten Experiments, in Order

Ranked by the ratio of what they would settle to what they would cost. The first two require no new data collection.

1. The onset-slope regression. In every longitudinal cohort with both reproductive history and incident dementia — UK Biobank, Framingham, Rotterdam, the Nurses' Health Study, Cache County, the Mayo Clinic Study of Aging — regress age at symptomatic onset on age at final menstrual period, restricted to incident cases, adjusted for birth cohort, education and *APOE*. A slope near one supports a menopausal clock; a slope near zero refutes it. This is a re-analysis of existing data and it is the single most informative thing anyone could do with this theory.

2. Reanalyse existing hormone trials against metabolic endpoints. Several completed trials collected imaging that has never been analysed as a bioenergetic outcome. Where FDG-PET, arterial spin labelling or magnetic resonance spectroscopy were obtained, test whether treatment altered cerebral metabolic rate rather than cognition. The theory predicts an effect on the first and none on the second; the existing analyses have only looked at the second.

3. The androgen-deprivation imaging study. Fifty men starting androgen deprivation for prostate cancer, fifty matched men with prostate cancer not receiving it, FDG-PET and 11C-acetoacetate PET at baseline and at eighteen months. Primary endpoint: change in regional cerebral glucose metabolism. Secondary: change in the ketone-to-glucose utilisation ratio. This gives the theory a male arm or takes it away, in under two years.

4. Dual-tracer imaging across the female transition. The single most important missing measurement. FDG-PET and ketone-tracer PET in the same pre-, peri- and post-menopausal women, longitudinally. If Stage I is a substrate switch, the ratio of ketone to glucose utilisation should *rise* across the transition and then plateau in women who compensate, and fail to rise, or rise and fall back, in those who do not. Nobody has imaged both fuels in the same brains across this window.

5. Myelin as the source, in humans. Myelin water imaging and diffusion metrics, with plasma and cerebrospinal-fluid markers of myelin lipid turnover, across the transition. The rodent finding is that brain ketones rise while plasma ketones fall. The human test is whether white-matter integrity declines in step with a rise in brain ketone utilisation, and whether exogenous ketosis prevents it.

6. The peri-menopausal ketogenic prevention trial. Randomise peri-menopausal women — irregular cycles, the population the submission itself specifies — to ketogenic medium-chain triglyceride supplementation or placebo for three years. Primary endpoint: change in regional cerebral glucose metabolism and white-matter integrity, not cognition. This is the trial the theory has been asking for since 2020 and it is directed at the intervention with the best safety profile and the best existing evidence.

7. Inherited reserve as the stratifier. Measure platelet cytochrome oxidase activity, corrected for citrate synthase, in a cohort of pre-menopausal women, and follow them through the transition with metabolic imaging. The prediction is that baseline peripheral complex IV capacity — reduced by around 30 per cent in adults with a maternal history of the disease — predicts who compensates. This unites the maternal-inheritance literature with the endocrine literature using an assay both have already used.

8. Wild-type tau and complex I, properly tested. Titrate wild-type human tau expression in primary neurons and in vivo, measuring complex I activity, ATP and mitochondrial dynamics across the range, and repeat with hyperphosphorylated wild-type tau. The question is whether the Alzheimer's form of tau sits with the normal protein or with the disease mutant on this axis. If it sits with the mutant, the loss-of-function reading is wrong; if it sits with the normal protein, tau-lowering therapies need a respiratory endpoint.

9. Respiratory-chain profiling as molecular staging. In autopsy series with both amyloid and tau staging, measure complex I and complex IV activity separately and test whether the ratio tracks the relative burden of the two pathologies, as the mouse dissociation predicts. This is a straightforward re-use of existing brain banks.

10. Estetrol, in the window. Before any further cell work, establish in an ovariectomised primate or in a peri-menopausal human pharmacodynamic study whether estetrol at tolerated doses changes cerebral glucose metabolism. The cell data are promising and the field's history in this area is a history of steroids that worked in cells.

Part VIII — Conclusion

33. What Anne Eckert Adds

A theory can be wrong in its central claim and still change what a field is able to think about. This one is, we judge, wrong in its central claim as stated — the menopause does not open a door, because in at least one identifiable group the door was ajar three decades earlier — and it nonetheless supplies three things the account of Alzheimer's disease did not have.

It supplies a place where the two proteins meet, with an address. Not "mitochondria are involved," which has been said for forty years, but complex I for tau and complex IV for amyloid, dissociable by genotype, synergistic on the membrane potential that both serve. That is a claim precise enough to be wrong, and it has so far been half-confirmed in human tissue and half-contradicted — which is what a useful claim looks like at this stage. It also generates a use nobody has made of it: if the two lesions have different addresses, the respiratory chain can be read as a record of which pathology has done more.

It supplies a date. This is the contribution that will outlast the theory. Alzheimer's disease is a disease whose beginning cannot be observed, and the whole apparatus of preclinical biomarkers exists to work backwards from an accumulation to an onset. The menopause is an exposure that announces itself: universal in half the population, dated by the patient, occurring at a median age near 51, preceding symptomatic disease by about the length of the prodrome, and — uniquely among the events in this disease — knowable in advance of anything happening. A field with no prospective starting gun has been handed one. Whether it is *the* starting gun is exactly the question the onset-slope regression in §32 would answer, and the fact that this regression has never been run is the most striking omission we found.

And it supplies a branch point where there was a cause. Every woman is exposed and most do not become ill; therefore the exposure is not the illness. Eckert says so, in one paragraph, with a figure, and then reverts to causal language. But the paragraph is right and it reorganises the problem. The disease becomes the failure of a compensation that everybody attempts — a switch from glucose to a second fuel, whose success in the rodent brain is bought by catabolising myelin, and whose human counterpart was imaged the year after she predicted it, as biomarkers stabilising and grey matter recovering and ATP production tracking preserved cognition. On that account the interesting women are the four-fifths who compensate, the interesting measurement is the ratio of ketone to glucose utilisation across the transition, and the interesting intervention is not the hormone at all.

That last conclusion is the practical one, and it is not the conclusion the paper draws. Of the four therapies it proposes, the one it argues for hardest — hormone replacement at the

peri-menopause — has been tested in randomised trials designed against precisely its specification and has produced nothing on cognition at four years and nothing at ten, with a national register reporting harm even among early initiators. The one it offers last, as a salvage for women who have missed the window, rests on a fact of unusual clarity: in mild Alzheimer's dementia the brain has lost an eighth of its glucose uptake and has lost nothing of its capacity to burn ketones. The glucose door is closing; the ketone door is open; and the intervention that walks through the open door needs no receptor system to have survived, carries no oncological liability, and is not restricted to one sex.

There is a version of the trials story in which the theory is simply mistaken, and intellectual honesty requires holding it open: hormone therapy looks protective in cohorts and does nothing in trials because the women who take it were going to do better anyway, and every timing gradient in the observational literature is the shadow of that one fact. The theory and the bias make almost the same predictions across the evidence that exists. They come apart on a metabolic endpoint, which no trial has used, in a peri-menopausal population, which no trial has enrolled.

The last thing to say is about the piece of evidence that has been sitting unused the longest. In 2012 this laboratory reported that wild-type tau *raises* complex I activity while the disease mutant lowers it — that the protein is bidirectionally linked to the organelle, protective in its normal form. Fourteen years on, that experiment has not been repeated in a neuron or in an animal, and tau-lowering therapies have reached human trials without a respiratory-chain endpoint among them. If the finding is right, the field is currently titrating away a mitochondrial regulator and measuring only the pathology it was hoping to remove.

The theory under review will probably not survive in the form its author gave it. Reformulated — the menopause as a scheduled, universal bioenergetic stress test whose outcome is set by reserve inherited down the maternal line — it survives, it is testable with existing cohorts and existing tracers, and it points at an intervention that is cheap, safe and unexamined. That is a considerable amount for ten pages to add.

References

Every reference below was verified against the PubMed record at the time of writing: author list, title, journal, year, volume and pagination were taken from the indexed entry rather than reconstructed, and the quantitative claims attributed to each source in the text were checked against its abstract or full text. PubMed identifiers are given so that any statement here can be traced to its origin in one step.

The primary document under evaluation is Anne Eckert, *Neuroendocrine and bioenergetic shift in women: an entry door for Alzheimer's disease* — a ten-page paper with six figures and 107 references, submitted in 2020 to an open scientific prize competition on the causes of Alzheimer's disease and not, as far as we can determine, subsequently published in a peer-reviewed journal. Quotations attributed to "the submission" throughout are from that document. Numbered references cited as belonging to its bibliography ("her reference 85", and so on) refer to the numbering of the submitted bibliography.

Where the text reports that the submission cites a source for a claim the source does not make, both documents were read in full before the discrepancy was recorded.

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