

The Unweighed
Element

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The Unweighed Element

Lithium as a Substrate of the Three-Phase Architecture of Alzheimer's Disease

A dissertation in the Adult Cognitive Disease corpus

Abstract

Twenty-seven metals were measured in the prefrontal cortex of 348 brains from the Religious Orders Study and the Rush Memory and Aging Project. One was significantly reduced in both mild cognitive impairment and Alzheimer's disease, and it was the one nobody had thought to weigh. Lithium sits in the human cortex at about two to four nanograms per gram — six orders of magnitude below potassium, three below rubidium, and a thousand-fold below the serum concentration a psychiatrist aims for. It is there in every brain, it is heterogeneously distributed, it correlates with episodic memory, and it accumulates inside amyloid plaques while falling in the tissue around them.

This volume takes that observation seriously and then refuses to take it on faith. It argues that endogenous lithium belongs in the corpus as a **Groundwork-level substrate** — not a phase of the disease but a condition the disease exploits, in the same class as calcium, the mitochondrion and the load-bearing lipid. It argues that the plaque's role as a sink for a scarce beneficial element is a genuinely new idea in a thirty-year-old literature that had only ever asked which toxic transition metals amyloid accumulates. And it argues that the most interesting joint the finding opens is one nobody has walked: reelin restrains glycogen synthase kinase-3 β through Dab1 and Akt, lithium is thought to restrain the same kinase, the corpus's Phase III is built on reelin's failure — and an exhaustive search returns five records for *reelin AND lithium*, none of them mechanistic.

Against all of that, the volume states four things plainly. The proposed mechanism does not survive a concentration calculation: endogenous cortical lithium is three to four orders of magnitude below its own inhibition constant at GSK-3 β , and the depletion that makes mice ill changes direct occupancy of that kinase by less than a hundredth of one per cent. The human measurement is thirteen months old and has not been independently replicated. The clinical record ran the other way in 2026: a two-year randomised trial in mild cognitive impairment missed all six of its co-primary endpoints, and the most recent meta-analysis, six trials and 394 participants, is negative. And the one design built to remove healthy-adherer bias from the observational literature — a target-trial emulation across 156,678 patients, by the author of the positive studies — found no dementia benefit at all.

The honest position is therefore narrower than the enthusiasm and wider than the scepticism. Endogenous lithium has a physiological function in the mammalian brain; cortical lithium is reliably lower in human MCI and AD; the deficit is at least partly downstream of the amyloid that sequesters it; whatever lithium does at nanomolar concentrations it does not do by occupying an active site; and the therapeutic corollary is unproven and currently unsupported by the best trial in the literature. That is a substrate claim, not a cure. It is graded as such throughout, and 78 claims are tabulated in a validity ledger with the experiment that would settle each one.



A note on what this volume is for

The corpus this dissertation joins holds that Alzheimer's disease is a process in time: a silent brainstem erosion from the third decade, a hippocampal bridgehead of microglia and matrix from the sixth, and a synaptic disintegration that is the first thing anyone sees. It holds that convergent autophagic collapse is the bottleneck those phases share, and that the plaque is a tombstone rather than a killer.

A new element arriving in that architecture has to do more than be interesting. It has to say where it sits, what it changes upstream and downstream, what it predicts that could fail, and what it costs the existing account if it is right. The four chapters of the first movement establish the element and the scale problem. Chapters V and VI take lithium to the corpus's own central mechanism — clearance and bioenergetics — and find it more complicated than advocacy allows. Chapters VII through XI walk it through each phase and each axis, grading the joints as strong, thin or absent on the evidence rather than on the elegance. Chapters XII through XIV are the human record: trials, salt, and the safety ceiling that constrains any prophylaxis proposal. Chapter XV is the case against, ranked by how much damage each objection actually does. Chapter XVI is the set of experiments that would decide it.

Where the literature is thin, this volume says the word *thin*. Where a search returned nothing, it reports the nothing. The metallome of Alzheimer's disease has produced three therapeutic programmes and one of them accelerated decline in the patients who received it; a fourth arriving on a cross-sectional correlation deserves the scepticism the first three earned.

PART ONE — THE ELEMENT AND THE SCALE

I. The Element Nobody Weighed

The metallome of Alzheimer's disease is one of the older literatures in the field and, until 2025, one of the most conceptually settled. It begins with a single observation: zinc above three hundred nanomolar destabilises solutions of human amyloid- β 1–40 and precipitates tinctorial amyloid, while the rat peptide, which binds zinc less avidly, is immune.¹ From that grew the metal hypothesis — that the neuropathogenicity of amyloid- β is promoted by, and perhaps dependent on, its interaction with transition metals.² Micro-proton-induced X-ray emission on amygdala from nine Alzheimer cases and five controls found zinc and iron significantly elevated in both the rims and the cores of senile plaques, and copper elevated in the rims.³ Cortical zinc was later shown to be more than doubled in Alzheimer's disease, scaling with tissue amyloid and with clinical severity, and — the sentence that mattered — "levels of other metals did not differ between groups."⁴

That sentence was true of the metals that were measured. The instruments and the frame both had a floor. Micro-PIXE, the modality that established the plaque-metal result, cannot detect elements lighter than sodium at all; Lovell's 1998 study was physically incapable of seeing lithium.³ The surveys that followed were designed around redox-active transition metals because those catalyse aggregation and Fenton chemistry, and alkali metals were surveyed separately and rarely.⁵ So the literature accumulated thirty years of evidence that amyloid plaques concentrate zinc, copper and iron, without ever asking whether they concentrate anything else.

1.1 What was actually found

Aron and colleagues assayed twenty-seven abundant and trace metals by inductively coupled plasma mass spectrometry in prefrontal cortex — Brodmann areas 9, 10 and 47 — from the Religious Orders Study and the Rush Memory and Aging Project, with cerebellum and antemortem serum in subsets.⁶ The largest single comparison is 348 brains: 177 with no cognitive impairment, 66 with mild cognitive impairment, 105 with Alzheimer's disease. A second cohort of frozen frontal cortex from the brain banks at Massachusetts General Hospital, Duke and Washington University provided 22 controls and 21 cases.

Of the twenty-seven metals, **lithium was the only one significantly reduced in prefrontal cortex in both MCI and AD**, and it carried the lowest adjusted probability of any metal in the disease-versus-control comparison. Both the total cortical concentration and the cortex-to-serum ratio fell. Three features of the result do more work than the headline.

The first is **regional specificity**. Lithium was not reduced in cerebellum — a relatively spared region carried in the same study as an internal control. A generic artefact of agonal state, nutrition or barrier failure ought not to respect Braak topography. This is the single strongest structural defence the finding has against reverse causation, and Chapter XV takes seriously the narrow counter-argument that

regional atrophy and regional barrier injury respect that topography too.

The second is that **serum lithium did not differ**. The deficit is brain-specific rather than systemic, which is why the authors report a cortex-to-serum ratio rather than an absolute concentration. That choice is well-founded: lithium reaches brain extracellular space within minutes and peaks there at about thirty minutes, but by twenty-four hours and at three weeks brain homogenate lithium significantly exceeds cerebrospinal fluid and dialysate, so intracellular brain lithium is poorly represented by plasma.⁷

The third is that **lithium in the surviving parenchyma correlated with cognition**. Lower lithium in the non-plaque cortical fraction tracked worse episodic memory, worse semantic memory and worse global cognition across the whole ageing population, and cortical lithium correlated with working memory and with the Mini-Mental State Examination. The correlation coefficients live in supplementary tables rather than the text, and the volume does not quote them.

1.2 The numbers, and what is not in the paper

Compartment	Untreated human	Therapeutic lithium
Prefrontal cortex	$2.36 \pm 1.23 \text{ ng g}^{-1}$, range 0.52–6.0 (ROSMAP controls); 3.50 ± 2.27 in the second cohort	0.23–0.55 mEq L ⁻¹ by ⁷ Li spectroscopy
Cerebellum	$2.90 \pm 1.69 \text{ ng g}^{-1}$	—
Serum	$1.53\text{--}10.41 \text{ ng mL}^{-1}$	0.6–1.2 mmol L ⁻¹

At an atomic mass of 6.94, 2.36 ng g^{-1} is about 340 nanomolar, and the observed control range of 0.52 to 6.0 ng g^{-1} spans roughly 75 to 865 nanomolar. The prior normal-brain dataset against which these are benchmarked measured sodium, potassium, lithium, rubidium and caesium across fourteen regions in 42 adults with no neurological history, and found lithium last in abundance order, markedly heterogeneous by region, highest in the caudate nucleus at $7.6 \pm 4.6 \text{ ng g}^{-1}$, lowest in brainstem and cerebellum, and — importantly for a disease of ageing — largely unchanged with age.⁸ In the human brain lithium sits about six orders of magnitude below potassium and three below rubidium.

Two honesty notes belong here rather than in a footnote. The paper reports numeric concentrations **only for its control groups**. The MCI and AD group means, and the percentage by which brain lithium falls in either, exist as plotted points in the figures and in the deposited source data, and appear nowhere in the text, methods or legends. No citable "brain lithium falls by X per cent in MCI" figure exists, and this volume does not manufacture one. Similarly, the magnitude of the human plaque-to-parenchyma lithium ratio is shown only in a figure panel.

1.3 Why the measurement is the contribution

It is worth being explicit that the achievement here is as much analytical-chemical as biological. At single-digit nanograms per gram the vessel, the acid, the water and the air in the hood are all plausible lithium sources. The protocol used pre-cleaned polyvinylidene fluoride vials soaked for at least

forty-eight hours in trace-grade nitric acid, ultra-trace reagents, and a fume hood dedicated to this work alone for the duration of the study; the homogenisation buffer was below $0.02 \mu\text{g L}^{-1}$ lithium and the phosphate-buffered saline below twenty-five parts per trillion. Indium was the internal standard, detection limits were set empirically from ten digestion blanks and twenty to thirty blank measurements per run, spike recovery ran 91 to 105 per cent, day-to-day duplicate correlation exceeded 0.99, and a laboratory member otherwise uninvolved relabelled every sample and held the key.

The reduction was then replicated three ways: in the second brain-bank cohort; in sixty cases reprocessed and run by a different laboratory at the University of Nebraska–Lincoln; and in forty-eight cases by an alternative dry-digestion protocol. The dry-to-wet tissue ratio was verified unchanged between groups — 0.127 ± 0.048 against 0.123 ± 0.034 — which forecloses the simplest objection, that Alzheimer cortex is merely drier.

This is better analytical hygiene than most of the metals-in-Alzheimer's literature, and a critique that leads with contamination will be dismissed. The uncomfortable corollary is that the human finding rests on a measurement very few laboratories are equipped to make, which is presumably why the authors replicated it three times before publishing, and which is part of why nobody has yet replicated it independently.



II. The Scale Problem

Everything difficult about this subject follows from one arithmetic comparison, so it is worth making it before anything else is built on top.

Lithium's inhibition constant at glycogen synthase kinase-3 β , measured directly in vitro, is **2 millimolar**.⁹ Its half-maximal inhibitory concentration at inositol monophosphatase from bovine brain is **0.8 millimolar**.¹⁰ At human phosphoglucomutase it is about **1.5 millimolar**;¹¹ at inositol polyphosphate 1-phosphatase, 0.5 to 6 millimolar depending on substrate.¹²

Endogenous human cortical lithium is **about 0.34 micromolar**.

The gap to GSK-3 β is therefore roughly six thousand-fold, or three to four orders of magnitude; the gap to inositol monophosphatase is about two and a half thousand-fold. The dose problem is not specific to the kinase. It is at least as bad for the inositol-depletion hypothesis, and it is worse for every other characterised target.

Sharpen it further. The depletion experiment that produces Alzheimer-type pathology in mice removes 92 per cent of dietary lithium, lowering serum lithium by 89 per cent and cortical non-plaque lithium by 47 to 52 per cent.⁶ In human-equivalent terms that moves brain lithium from roughly 0.34 to roughly 0.17 micromolar. Against an inhibition constant of 2 millimolar, that change alters direct fractional occupancy of GSK-3 β by **less than one hundredth of one per cent**. Direct competitive inhibition is not

carrying this effect, and it cannot be made to.

The authors say so themselves, in the paper, in terms this volume can only endorse: "the reported IC_{50} of the Li-GSK3 β interaction in vitro is in the millimolar range, making this a seemingly unlikely interaction at the low micromolar concentration range of endogenous Li in the brain."⁶

2.1 What the scale problem forecloses

It forecloses the sentence "lithium deficiency causes Alzheimer's disease by releasing GSK-3 β from inhibition," if that sentence is meant stoichiometrically. It forecloses any inference from the therapeutic lithium literature — where brain concentrations are three orders of magnitude higher — to the endogenous range, without an argument for why the mechanism should be the same. And it forecloses the most natural reading of the epidemiology, because a dose-response in drinking water that spans 0.5 to 160 $\mu\text{g L}^{-1}$ is a dose-response in a range where no characterised lithium target is meaningfully occupied.

It also forecloses something on the other side of the ledger. At therapeutic brain concentrations of 0.23 to 0.47 millimolar, lithium sits **below the IC_{50} of every one of its characterised targets**. On a single-site model that is roughly 22 to 37 per cent inhibition of inositol monophosphatase, 13 to 24 per cent of phosphoglucosyltransferase and 10 to 19 per cent of GSK-3 β — partial inhibition of a structurally related family, in parallel, with nothing selectively engaged. The dose gap and the promiscuity problem are the same problem seen from two sides: lithium is promiscuous at therapeutic doses precisely because therapeutic doses are sub- IC_{50} for everything.

2.2 What the scale problem leaves standing

Three legitimate arguments survive, and the volume needs all three.

The magnesium argument. Lithium inhibits GSK-3 by competing with magnesium, not with ATP or with peptide substrate.¹³ Because cellular ATP exceeds free magnesium and chelates it, the authors of that work concluded explicitly that lithium "will have a greater effect on GSK-3 activity in vivo than expected from in vitro studies." A subsequent dual-inhibition analysis with beryllium established two distinct magnesium sites, one lithium-sensitive and one not.¹⁴ The theoretical case for why a monovalent ion can displace a divalent one in some enzymes and not others has been worked out: it turns on the net charge of the metal complex and the solvent exposure of the cavity.¹⁵ All of this is directionally right. None of it is quantitatively specified — nobody has published a measured inhibition constant for lithium at GSK-3 β at physiological free magnesium in a neuron — and a directional correction does not close a six-thousand-fold gap.

The regulatory argument, which is the one the paper actually makes. Aron and colleagues do not claim that 0.3 micromolar lithium occupies the catalytic site. They report that lithium deficiency **raises GSK-3 β expression** — total protein elevated in CA1 neurons, oligodendrocytes and microglia, confirmed by proteomics, with *Gsk3b* messenger RNA elevated — and **raises its activation state**, with activating autophosphorylation at tyrosine 216 significantly increased and the inhibitory serine-9 to total ratio falling. Tau, a substrate, shows a three- to four-fold rise in phosphorylation at serine 202 and at serine

396/404. The claim is that endogenous lithium status sets the abundance and activation of the kinase, not that it titrates its active site. That is a materially different claim, and it is not subject to the occupancy objection. It is, however, a claim with an unidentified proximal target: something lithium-sensitive at nanomolar concentrations regulates GSK-3 β transcription and activation, and nobody knows what it is.

The indirect-signalling argument. Lithium's effect on GSK-3 in vivo is substantially protein-complex-mediated. Lithium regulates Akt/GSK-3 signalling and GSK-3-dependent behaviour by disrupting a complex of Akt, β -arrestin-2 and protein phosphatase 2A; in β -arrestin-2 knockout mice, lithium fails to affect that signalling or to produce its behavioural effects at all.¹⁶ Separately, the rise in inhibitory serine-9 phosphorylation after lithium is caused by inhibition of GSK-3 itself, in an autoregulatory loop running through a GSK-3-dependent protein phosphatase-1 and inhibitor-2 complex — one inhibitor with two inhibitory actions, acting in concert to amplify a modest direct effect.^{17,18} Amplification is exactly what the dose gap requires. Whether it amplifies by four orders of magnitude is not established.

2.3 The honest formulation

The formulation this volume defends, and repeats wherever the mechanism is at issue, is this. **Endogenous lithium status sets the expression and activation state of GSK-3 β by a route that is not direct active-site occupancy and has not been identified.** GSK-3 β then sits downstream of the lesion, which is why two structurally unrelated inhibitors of it reverse the depletion phenotype. A rescue downstream of a lesion locates the lesion's consequence; it does not identify the lesion's target. If lithium's proximal target is upstream and unknown, then the mechanism as published is: *unknown lithium-sensitive node* $\rightarrow$ *GSK-3 β derepression* $\rightarrow$ *pathology*. That is weaker and less specific than the abstract's claim, and it is the version the evidence supports.

III. What Lithium Actually Does

Lithium is routinely used as though it were a selective inhibitor of glycogen synthase kinase-3. It is not, and the people who discovered its action on that kinase said so. Writing in 2003, the Klein laboratory noted that lithium "also inhibits other targets, including inositol monophosphatase and structurally related phosphomonoesterases, and thus additional approaches are needed to attribute a given biological effect of lithium to a specific target."¹⁷ Very little of the Alzheimer lithium literature meets that standard.

3.1 A target class, not a target with off-targets

The right way to describe lithium's pharmacology is not one target with a list of exceptions. It is a **structurally defined enzyme family**, united by a common tertiary fold and by inhibition through the same ion-cofactor competition, at overlapping concentrations.^{19,20} Inositol monophosphatase, inositol polyphosphate 1-phosphatase, 3'-phosphoadenosine-5'-phosphate phosphatase and their relatives share a core fold; lithium is an uncompetitive inhibitor with respect to substrate and non-competitive with respect to magnesium across the whole family.

Target	Potency	Mechanism
Inositol monophosphatase	IC ₅₀ 0.8 mM	Uncompetitive; traps the phospho-enzyme intermediate
Human phosphoglucomutase	IC ₅₀ ~1.5 mM	Competitive with Mg ²⁺
Glycogen synthase kinase-3β	K _i 2 mM	Competitive with Mg ²⁺
Inositol polyphosphate 1-phosphatase	K _i 0.5–6 mM by substrate	Uncompetitive
BPNT1 / PAP phosphatase	Inhibited at subtherapeutic doses	Same fold

The uncompetitive kinetics at inositol monophosphatase are more interesting than they look. Because inhibition *increases* with substrate flux, lithium preferentially damps an over-active phosphoinositide cycle and is self-limiting where flux is low.^{10,21} That is the basis of the use-dependence argument, and it is the best pharmacological reason to expect a drug at sub-IC₅₀ concentrations to act selectively on a system that is already failing — a theme that returns in Chapter VI, where lithium's mitochondrial effect turns out to appear only in diseased neurons.

The mechanism at that enzyme is worked out to the residue. Lithium inhibits by trapping a phosphorylated intermediate and preventing its hydrolysis,²¹ and site-directed mutagenesis of nine active-site residues shows lithium and magnesium share a binding site: mutations at lysine 36, aspartate 90, threonine 95, histidine 217 and cysteine 218 reduce affinity for both in parallel.²²

3.2 A target that is neither kinase nor inositol phosphatase

The cleanest demonstration that lithium can produce a selective neuronal phenotype through something else entirely comes from a nematode. Loss of BPNT-1 in *Caenorhabditis elegans* causes dysfunction of a single bilateral neuron pair — the ASJ chemosensory neurons — with matching behavioural deficits in dauer exit and pathogen avoidance. Acute lithium reproduces this, reversibly, specifically through BPNT-1 inhibition, and the selectivity arises from the restricted expression of a cytosolic sulfotransferase.²³ The mechanism is accumulation of a toxic metabolite, not modulation of a signalling cascade; in yeast, loss of the same enzyme or lithium exposure produces more than an eighty-fold accumulation of 3'-phosphoadenosine-5'-phosphate and potent growth inhibition, rescued dose-dependently by expressing the human enzyme.¹⁹

A second member of the family reaches directly into the corpus's seventh axis. BPNT2 is a Golgi bisphosphate nucleotidase, directly inhibited by lithium, that metabolises the by-products of glycosaminoglycan sulfation. Nervous-system-specific knockout reduces total glycosaminoglycan sulfation across brain regions and specifically lowers chondroitin-4-sulfate with a compensatory rise in chondroitin-6-sulfate in cortex and hippocampus.²⁴ The 4-sulfate to 6-sulfate ratio is precisely the parameter that governs how strongly a perineuronal net restricts plasticity. The authors are careful that these changes did not produce gross alterations in the nets themselves and that behaviour was unremarkable — but the existence of a direct lithium-sensitive enzyme setting chondroitin sulfation pattern in the hippocampus is a mechanistic handle that nobody has connected to disease. Chapter X

returns to it.

Even a single target propagates. At six millimolar in yeast, lithium inhibits protein synthesis at initiation, accumulating 80S monosomes and dissociating eIF4A from ribosomal subunits, and the conditions that reverse phosphoglucosylase inhibition also reverse the translation block.²⁵

3.3 The substrates that matter, graded

Tau: strong, with epitope specificity. GSK-3 β transfected into cells stably expressing individual human tau isoforms hyperphosphorylates tau at all the paired-helical-filament-diagnostic epitopes tested.²⁶ The epitope resolution is unusually good: in differentiated neuroblastoma, lithium reduces phosphorylation at threonine 181 and at serine 396/404, so GSK maintains those, while serine 262 and 356 — the KXGS sites in the microtubule-binding repeats — are driven by protein kinase A and are not GSK-maintained.²⁷ GSK-3 is therefore not the kinase for the microtubule-detaching sites, which is a real constraint on how much of tau's dysfunction it can explain. Functionally, lithium in human neurons reduces tau phosphorylation, enhances tau-microtubule binding and promotes microtubule assembly.²⁸ Conditional GSK-3 β overexpression in adult mouse forebrain produces reduced nuclear β -catenin, tau hyperphosphorylation, somatodendritic pretangle tau, reactive gliosis and dying granule cells.²⁹

The complication is important. Long-term lithium at relatively low therapeutic concentrations reduced tau lesions in tauopathy mice "primarily by promoting their ubiquitination rather than by inhibiting tau phosphorylation."³⁰ If the therapeutic-range benefit runs through the ubiquitin-proteasome system rather than kinase inhibition, the GSK-3 account is not doing the work it is credited with.

Amyloid: contested, and formally rebutted. The claim that therapeutic lithium blocks amyloid- β production by interfering with γ -secretase cleavage of the amyloid precursor protein, through GSK-3 α rather than β , was published in *Nature* in 2003.³¹ It was contradicted in the same journal in 2011 by a group that analysed processing of mouse and human APP in vivo across five genetic and viral models and stated that their data "do not yield evidence for either GSK-3 α -mediated or GSK-3 β -mediated control of APP processing in brain in vivo."³² Woodgett, who co-discovered lithium's inhibition of GSK-3, is a co-author of the rebuttal. The best-characterised dual-pathology mouse agrees with the rebuttal: chronic lithium in aged 3xTg-AD mice reduced tau phosphorylation, **did not significantly alter amyloid load, and did not improve working memory despite the phospho-tau reduction.**³³ That triple dissociation — kinase engaged, tau moved, amyloid unmoved, behaviour unmoved — is the tightest in-model result in the literature and Chapter XV returns to it.

β -catenin and Wnt: mechanistically strong, weak as an Alzheimer mechanism. Lithium activates downstream Wnt components and accumulates β -catenin, attributable to GSK-3 β inhibition,³⁴ and an Axin-derived peptide inhibitor reproduces the effect, which is the correct methodological template for proving a GSK-3-mediated action.³⁵ Whether Wnt repression is a driver of sporadic Alzheimer's disease rather than a consequence is not established, and Chapter VIII shows that the same β -catenin stabilisation predicts the *opposite* of what is wanted in oligodendrocytes.

3.4 The negative control the field already ran

The strongest argument against a GSK-3-mediated mechanism is not theoretical. It is that somebody built a selective, brain-penetrant, irreversible GSK-3 β inhibitor, reproduced the entire lithium preclinical package with it, and took it into three trials.

Tideglusib is a thiadiazolidinone acting at or near cysteine 199, with a dissociation rate constant not significantly different from zero, and it does not inhibit a panel of other kinases carrying a homologous active-site cysteine.³⁶ Sustained oral dosing in animals decreased tau hyperphosphorylation, lowered plaque load, improved learning and memory and prevented neuronal loss.

Trial	Design	n	Result
Pilot, AD	Double-blind, escalating 400–1000 mg, 20 weeks	30	Positive trends, none significant; transaminase rise in six active cases
ARGO, phase II AD	Four arms, 26 weeks, 55 sites	306	No significant difference from placebo on any efficacy variable
TAUROS, phase II PSP	600/800 mg vs placebo, 52 weeks	146	No difference on primary or any secondary endpoint

ARGO's primary outcome, the cognitive subscale of the Alzheimer's Disease Assessment Scale, was negative, with dose-dependent reversible transaminase elevation in nine to sixteen per cent of treated patients.^{37,38} The progressive supranuclear palsy trial found nothing clinically, although its magnetic resonance substudy of thirty-seven patients showed significantly less atrophy progression on drug — whole brain -1.3 ± 1.4 per cent against -3.1 ± 2.3 per cent — with no clinical correlate whatsoever.^{39,40} A power analysis across 187 placebo-assigned patients from that trial and another later established there was no detectable placebo effect on the rating scale and that fifty-one patients per group would detect a halving of annual progression,⁴¹ so TAUROS was adequately powered for a large effect and genuinely saw none.

And then the dissociation. A meta-analysis of five randomised trials in Alzheimer's disease and mild cognitive impairment, 568 patients, found no overall effect of GSK-3 inhibitors on cognition — standardised mean difference -0.25 , $p = 0.11$ — but **split cleanly by agent: lithium -0.41 , $p = 0.04$; tideglusib -0.02 , $p = 0.89$.**⁴²

There are two readings and the volume presents both. On the first, this falsifies the mechanism: if GSK-3 inhibition were operative, the selective agent should have matched or beaten the promiscuous one, and it did the reverse. On the second, it vindicates polypharmacology, and Chapter V supplies the mechanistic basis — because lithium's two principal targets push the autophagic machinery in *opposite* directions, a pure GSK-3 inhibitor is not a cleaner lithium but half a lithium, delivered without the arm that may matter and with the arm that may hurt. Three caveats have to be stated for either reading to be honest: tideglusib ran 26 weeks in mild-to-moderate disease where lithium's positive signals came from twelve to twenty-four months in amnesic MCI; brain target engagement was never confirmed; and effect size in that meta-analysis was associated with study duration.

IV. The Plaque as a Sink

If the metallome literature had a single organising idea, it was that amyloid accumulates metals that are toxic. Four lines of evidence in Aron and colleagues make the opposite case for one element: that the plaque removes something beneficial from the tissue around it.

Mapping. Laser-ablation ICP-MS with a 213-nanometre laser, ^7Li normalised to ^{13}C to correct for ablated mass, matrix-matched standards made by spiking and refreezing homogenised tissue, and an adjacent immunostained section computationally superimposed on the lithium matrix. "A highly significant concentration of Li in A β plaques was detected in every case of MCI and AD, which increased from MCI to AD."⁶ The limit of quantification for ^7Li in that modality was 0.82 ng g^{-1} . Iron, copper and zinc were carried as positive controls and were all enriched in plaques — the method reproduces the classical result while adding the new element.

Subfractionation. A modified detergent protocol separating a soluble non-plaque fraction from a plaque-enriched pellet, with homogenisation buffer below $0.02 \text{ } \mu\text{g L}^{-1}$ lithium and washes below twenty-five parts per trillion, found lithium in the prefrontal non-plaque fraction significantly reduced in Alzheimer's disease.

Genetic and temporal ordering. In J20 amyloid-precursor-protein transgenic mice at twelve months, lithium was concentrated three- to four-fold in cortical amyloid deposits relative to adjacent plaque-free cortex, and non-plaque cortical lithium was significantly reduced against wild-type. At three months, **before amyloid deposition begins**, it was not. This is the cleanest ordering argument in the paper: the parenchymal deficit follows the plaques.

Binding. Equilibrium dialysis with synthetic amyloid- β 1–42 shows lithium binds both fibrils and oligomers, saturably, with a high-affinity range that includes the physiological brain and serum range and a lower-affinity range corresponding to clinical doses. The dissociation constants are in a supplementary table and are not quoted here.

4.1 What this does to the tombstone claim

The corpus holds that the plaque is a tombstone: a marker of a cell that has already failed, not the agent of failure. That claim has always had to absorb the awkward fact that plaques are not inert objects — they bind zinc, copper and iron, they nucleate a microglial response, they are physically disruptive. What it has not had to absorb is a mechanism by which the plaque is **harmful without being neurotoxic**.

That is what sequestration supplies, and it is worth stating precisely because it is a friendly amendment rather than a refutation. On this account the plaque does not poison the neuron. It acts as a sink for a scarce element that the surrounding tissue needs, lowering the concentration available to the cells that are still alive. Nothing about that requires amyloid to be a toxin. It requires amyloid to be an adsorbent. A

tombstone made of blotting paper is still a tombstone, and it can still dry out the ground around it.

The corpus currently has no category for this. Its vocabulary for the plaque is *marker*, *consequence*, *gravestone*; it does not have *sequestrant*. Adding one is the single most consequential revision this volume proposes to the existing architecture, and it is graded **moderate** rather than strong, for the reason in the next paragraph.

4.2 The inversion the authors' own model creates

If amyloid sequesters lithium, then the lithium deficit in human Alzheimer brain is **at least partly downstream of amyloid deposition**. The mouse data make this explicit: the deficit is absent at three months and present at twelve, appearing after plaques do.

This is a genuine problem for the volume's own framing, and it cannot be argued away. The paper is titled *Lithium deficiency and the onset of Alzheimer's disease*, and the human observation is offered as evidence that the deficiency is upstream. But the mechanism the same paper proposes for why the deficit deepens from MCI to AD is that there is more amyloid to adsorb the element. Those two claims pull in opposite directions. The most that can be defended is a two-stage account: a **primary** component of low brain lithium — dietary, geographic, or set by whatever unidentified regulation governs the cortex-to-serum ratio — which is upstream and which the mouse depletion experiment models; and a **secondary**, amplifying component produced by sequestration once deposition begins, which is downstream and which makes the deficit progressive. A feed-forward loop of that shape is biologically plausible and entirely untested, and the human data cannot presently distinguish it from a purely downstream deficit.

The volume therefore grades the two halves differently. That endogenous brain lithium is lower in MCI and AD, and that it is concentrated in plaques: **strong**, on a large blinded measurement replicated three ways. That the deficit is causally upstream in human disease: **weak**, and Chapter XV sets out why the study design cannot establish it.

4.3 The cautionary precedent

One reason for that grading is a track record. Every attempt to translate the metal hypothesis into a therapy has stalled or backfired.

Clioquinol, a metal-protein attenuating compound, reduced brain amyloid deposition by 49 per cent in transgenic mice — a decrease of $375 \mu\text{g g}^{-1}$ wet weight, blinded, $p = 0.0001$.⁴³ Its pilot clinical trial randomised 36 patients, and the benefit was confined to a more severely affected subgroup and driven by placebo-group worsening.⁴⁴ Its successor, PBT2, in 78 patients over twelve weeks, lowered cerebrospinal amyloid- β 42 by 56.0 pg mL^{-1} and produced cognitive effects on two executive sub-tests out of a full battery;⁴⁵ the follow-up imaging trial found no significant difference from control at twelve months on amyloid positron emission tomography, and none on fluorodeoxyglucose imaging, volumetrics, blood biomarkers or cognition.⁴⁶

And then deferiprone. Brain iron is elevated in Alzheimer's disease and cerebrospinal ferritin predicts decline over seven years.⁴⁷ In a twelve-month randomised trial of 81 amyloid-confirmed patients, deferiprone **engaged its target** — hippocampal iron fell on quantitative susceptibility mapping — and the treated group **declined faster**, with an interaction coefficient of -0.50 (95% CI -0.80 to -0.20), increased frontal volume loss and 7.5 per cent neutropenia. The authors' conclusion was that "lowering iron with deferiprone is detrimental to patients with AD."⁴⁸

This does not falsify the lithium hypothesis. The direction is opposite — repletion of a deficient element rather than chelation of an excess one — and the preclinical data here are considerably stronger than deferiprone's were. But it establishes three things a serious volume cannot omit. Metal dysregulation in Alzheimer brain is abundant and has never once yielded a working intervention. **Confirmed target engagement is not evidence of benefit.** And the same senior investigator authored clioquinol, PBT2, deferiprone and the *Nature* commentary accompanying the lithium paper — which is a reason to read his caveats carefully rather than a reason to discount them.

PART TWO — THE BOTTLENECK

V. The Clearance Arm

This is the chapter the corpus most needs and the one where advocacy is most dangerous, because the corpus's central claim is convergent autophagic collapse and lithium is the best-characterised mTOR-independent lever on that bottleneck in pharmacology. The temptation is to write that sentence and stop. The evidence does not permit it.

5.1 The positive case

Lithium induces autophagy by inhibiting inositol monophosphatase, depleting free inositol and lowering inositol 1,4,5-trisphosphate, independently of mTOR.⁴⁹ The experiment is thorough and the details matter. Ten millimolar lithium chloride, with ten millimolar sodium chloride as an osmotic control that did nothing, cleared aggregate-prone substrates: huntingtin exon 1 with 74 polyglutamine repeats, and the A53T and A30P α -synuclein mutants, in inducible lines with the transgene switched off and clearance followed for 120 and 24 hours respectively. LC3-positive vesicles and LC3-II rose comparably to 0.2 micromolar rapamycin. Three-methyladenine abolished the effect completely; the proteasome inhibitor lactacystin did not, so the route is autophagic.

Target identification was done properly. A specific inositol monophosphatase inhibitor at 100 micromolar reproduced every lithium effect. The GSK-3 β inhibitor SB216763 at ten micromolar **did not** — it *increased* huntingtin aggregates and *slowed* mutant α -synuclein clearance. Rescue confirmed the node: myo-inositol at one millimolar, or a prolyl endopeptidase inhibitor, each raised inositol trisphosphate and reversed lithium's protection, while reversing nothing about rapamycin's. And mTOR independence was measured rather than assumed — neither lithium nor the inositol monophosphatase inhibitor reduced phosphorylation of S6 kinase 1, S6 or 4E-BP1, while rapamycin did, and lithium still cleared aggregates in cells overexpressing Rheb.

Tau is a substrate of this. In tauopathy mice given oral lithium chloride for four months from five months of age, sensorimotor scores improved, tau phosphorylation and soluble tau fell, tangle number fell, LC3-positive puncta increased in neurons and p62 protein decreased — genuine flux rather than a block.⁵⁰ In human neuroblastoma seeded with post-mortem brain seeds, forty-eight hours of lithium reduced sarkosyl-insoluble tau, reduced p62 and raised LC3-II, and **an inositol monophosphatase inhibitor reproduced the effect**, which is the pharmacological separation of the autophagic arm from the phosphorylation arm.⁵¹ That study also found the effect was strain-dependent: lower with corticobasal degeneration seeds than with Alzheimer or progressive supranuclear palsy seeds — the same drug, cell and concentration, different conformer, different clearance.

One observation in the tauopathy mouse work deserves to be lifted out, because it is a direct morphological datum for the tombstone thesis and it has been under-cited for fourteen years.

Tangle-containing neurons were completely LC3-negative, while the LC3-positive autophagosome-like puncta contained phospho-tau.⁵⁰ The autophagic machinery engages the soluble and pre-tangle species. The mature deposit sits outside the degradative system altogether. Whatever the tangle is, it is not what the clearance apparatus is working on.

5.2 The complication, which is fatal to any simple story

Two years after establishing the inositol arm, the same laboratory reported that lithium's two targets act in **opposite directions** on the same readout: "In contrast to IMPase inhibition that enhances autophagy, GSK3 β inhibition attenuates autophagy and mutant huntingtin clearance by activating mTOR."⁵² Their proposed resolution was to add rapamycin, so that autophagy is driven by an mTOR-independent route while rapamycin cancels the mTOR activation lithium's own GSK-3 arm causes; in a fly model of Huntington's disease the combination outperformed either arm alone.

Lithium therefore carries an autophagy-suppressing arm inside itself, and the net direction depends on which target dominates in a given cell at a given concentration. A review of the field puts the consequence plainly: lithium enhances degradation of mutant huntingtin, phospho-tau and α -synuclein, "while in a mouse model of cerebral ischemia and Alzheimer's disease autophagy downregulation by lithium is observed."⁵³

This is not a footnote. It is the most useful thing in the chapter, because it is the cleanest published demonstration that a single agent can have an internally contradictory effect on the corpus's own bottleneck — and therefore that **autophagic capacity, rather than the aggregate, is the variable of interest**. It also reconciles tideglusib's failure with lithium's possible success without requiring either result to be wrong.

5.3 The level problem: two arms at two levels of one pathway

There is a more interesting reading available than "one arm up, one arm down," and it is defensible from two papers.

Inhibition of GSK-3 reduces amyloid precursor protein expression by enhancing its degradation, driven by an increase in the number of lysosomes, and that induction is associated with nuclear translocation of TFEB, the master regulator of lysosomal biogenesis; net amyloid- β falls.⁵⁴ If that holds, then lithium's GSK-3 arm — the arm that suppresses macroautophagy via mTOR — may simultaneously **expand lysosomal capacity**. The two targets would then not be simply pro and anti, but acting at **different levels of the same pathway**: inositol monophosphatase on autophagosome formation, GSK-3 on lysosomal supply.

That framing maps directly onto the Nixon endolysosomal programme, where the Alzheimer lesion sits at the degradative rather than the sequestration end, and it implies that it is lithium's GSK-3 arm, not its inositol arm, that speaks to the actual human lesion. One honesty point must accompany it every time it is stated: that study used specific GSK-3 inhibitors and small interfering RNA, **not lithium**. "Lithium activates TFEB" is an inference, not a finding, and it is graded as such in the ledger.

5.4 Two counter-data that must not be buried

Lithium interferes with the vacuolar ATPase and blocks lysosomal acidification. In tumour-reactive CD8⁺ T cells, cytoplasmic lactic acid increases proton pumping into lysosomes, and lithium carbonate "interfered with vacuolar ATPase to block lysosomal acidification," rescuing a lysosomal diacylglycerol-protein kinase C θ signal that relocalises a lactate transporter to mitochondria.⁵⁵

In neuronal terms, a drug that interferes with the v-ATPase and blocks lysosomal acidification is doing what bafilomycin does — and lysosomal de-acidification is precisely the lesion the corpus places at the centre of convergent autophagic collapse. If lithium does this in neurons at achievable concentrations, the argument for lithium-as-clearance-rescue **inverts**. The cell type is different, the metabolic context is a tumour microenvironment with high extracellular lactate, and the concentration is not stated in the abstract. But the mechanism is specific and it is on the v-ATPase. **Nobody has tested it in neurons.** That is named here as an explicit gap and as the single highest-priority experiment in this chapter.

Lithium inactivates the 20S proteasome. Lithium chloride inactivates both the chymotrypsin-like and the peptidyl-glutamyl peptide hydrolysing activities of the purified 20S proteasome, time-dependently, without affecting non-proteasomal proteases, with half-lives for inactivation at ten millimolar of about 23 and 36 minutes; only partial activity recovers after dialysis.⁵⁶

The implication for the literature is uncomfortable. If lithium at ten millimolar half-inactivates the proteasome within twenty-three minutes, then a substantial part of the "enhanced clearance of aggregate-prone protein at 10 mM" corpus is being measured in cells whose *other* degradative system is being switched off. The original autophagy work controlled in the right direction — lactacystin did not block lithium's effect, and the inositol rescues had no proteasomal effect on a ubiquitin-GFP reporter — but it did not test lithium itself on that reporter. The defensible statement is therefore: **lithium may shift proteostatic burden from the proteasome onto autophagy**, which is a different claim from lithium enhancing proteostasis. The study is in a non-neuronal leukaemia line, and that is stated.

5.5 Where the chapter lands

For the corpus, the finding is this. Lithium is a real, mTOR-independent lever on the autophagic bottleneck; it acts on tau in vivo through that lever; and it does so by the **inositol** arm, not the kinase arm — which is awkward, because the endogenous-deficiency mechanism in Chapter II runs through the kinase and the paper reports that inositol itself was **not altered** by endogenous lithium deficiency. That dissociation is worth stating in full: the arm of lithium's pharmacology that touches the corpus's central mechanism most directly appears **not** to be the arm that endogenous lithium deficiency operates on.

So the clearance chapter does not support the claim that endogenous lithium deficiency causes autophagic collapse. It supports a different and narrower claim: that **pharmacological** lithium is a two-armed, level-specific, net-uncertain modulator of the clearance machinery, worth studying on its own terms, with an unresolved v-ATPase liability and an unexamined proteasomal one.



VI. The Bioenergetic Arm

The mitochondrial evidence is better than the clearance evidence in one specific and important respect: it includes human tissue, it peaks at a therapeutic concentration, and it shows a conditional effect that fits the corpus's substrate logic unusually well.

6.1 Human brain tissue, and a peak at one millimolar

Post-mortem human cortical homogenates exposed *ex vivo* to lithium up to ten millimolar showed a dose-dependent increase in respiratory chain complex activity with a **maximum at 1 mM**: complexes I+III at 165 per cent of control ($p = 0.03$), complexes II+III at 146 per cent ($p = 0.00002$). Succinate dehydrogenase was unchanged up to two millimolar. **Complex IV was not significantly affected** — a twelve per cent decrease at one millimolar, $p = 0.4$.⁵⁷

A peak at a therapeutic rather than a supraphysiological concentration is rare in this literature and should be said plainly. It is also the only human-tissue mitochondrial datum available.

6.2 The conditional effect

Primary hippocampal neurons from 3xTg-AD embryos and from wild-type controls were assayed on an extracellular flux analyser with lithium chloride at 0, 0.1, 1 and 10 millimolar for twenty-four hours.⁵⁸ Baseline, the Alzheimer-model neurons had significantly lower basal respiration, lower maximal respiration and lower spare respiratory capacity, with coupling efficiency unchanged.

Then the result that matters: **lithium had no effect on any bioenergetic parameter in control neurons** — not basal or maximal respiration, spare capacity, coupling efficiency, ATP, cytochrome oxidase activity, or any complex subunit. In the disease-model neurons it produced a dose-dependent rise in oxygen consumption, significant at 1 and 10 millimolar, with increased basal and maximal respiration, increased spare capacity and increased total ATP. At one millimolar there were selective increases in NDUFB8, MT-CO1 and ATP5A — complexes I, IV and V — with complexes II and III unchanged, and increased cytochrome oxidase activity.

Lithium here is not a stimulant. It is restorative, and only where the system has already failed. That is precisely the shape the corpus's substrate framework predicts for a use-dependent, sub-IC₅₀ inhibitor of a family of enzymes whose inhibition scales with substrate flux (Chapter 3.1), and it is the strongest internal consistency in this volume.

One flaw in that paper has to be reported, because a reviewer will find it. The results and abstract report ten millimolar as producing significant increases, while the discussion argues at length that ten millimolar is supraphysiological and produces "suppression of OCR and ATP production, together with reduced cytochrome c oxidase activity," framing it as a stress test defining the upper limit of tolerance. The volume cites the one-millimolar data and flags the discrepancy rather than choosing a side.

The conditionality has independent human support. In induced pluripotent stem-cell-derived neural precursors from lithium-responsive patients, non-responsive patients and controls, lithium regulated 554 genes uniquely in the responder cells, enriched for spliceosome and oxidative phosphorylation, and **improved oxygen consumption only in responder cells**.⁵⁹ And in whole-blood transcriptomes from fifty lithium-treated patients, a 46-gene co-expression module correlated with response, with 43 of the 46 reduced in better responders and the central regulators all mitochondrially encoded — MT-ND1, MT-ATP6, MT-CYB — with oxidative phosphorylation the over-represented process.⁶⁰ That correlation is nominal only ($r = -0.299$, $p = 0.035$) and is reported as such.

6.3 The calcium arm, and a clean negative for GSK-3

Isolated brain mitochondria in a lithium chloride medium resist calcium-bolus-induced swelling, depolarisation and cytochrome c release; under slow calcium infusion lithium increases the calcium capacity of both synaptic and non-synaptic brain mitochondria before sequestration fails.⁶¹ The target is the permeability transition: cyclosporin A, sanglifehrin A and magnesium each raise calcium capacity in potassium medium but fail to do so in lithium medium, which is occlusion at a shared target, and lithium protects even in the presence of ATP where cyclosporin A is reported ineffective. The effect is ion-specific — absent when mitochondria are challenged with strontium instead of calcium — and, decisively for this volume's argument, **it is not GSK-3 β** : SB216763 and SB415286 did not increase calcium capacity.

This is an ion-substitution experiment rather than a pharmacological dose-response, so it says nothing about therapeutic concentrations. It says something better for a substrate argument: that lithium has an action on the mitochondrial permeability transition that is independent of every signalling target in Chapter III, and that connects directly to the corpus's treatment of calcium as a first principle. The systemic counterpart is old and almost forgotten: in 186 rats sampled around the clock, lithium raised serum calcium, serum and cerebellar magnesium and parathyroid hormone, lowered calcitonin, and **altered the temporal pattern of all four**, which the authors read as competition for calcium receptor sites forcing a compensatory shift to a higher calcium set-point.⁶²

A second mitochondrial mechanism is genetically established. Long-term lithium raises cell respiration rate, mitochondrial membrane potential and mitochondrial oxidation, and protects in vivo against methamphetamine-induced mitochondrial toxicity, preserving cytochrome c, the Bcl-2 to Bax ratio and cytochrome oxidase activity — and **Bcl-2 knockdown abolishes the lithium-induced increase in mitochondrial oxidation**.⁶³ That is a necessity test, not a correlation.

6.4 Two cautionary datasets and one honest absence

In human neuronal-like cells at 2.5 millimolar, lithium **reduced** the expression of citric-acid-cycle genes with no positive effect on oxidative phosphorylation gene expression, while in microglia from the same study it **increased** oxidative phosphorylation gene expression.⁶⁴ Cell-type dependence, and a negative result in neurons that does not fit the simple story. It belongs alongside the conditional-effect data, not after them.

Second, under mild complex I inhibition with rotenone in a neuronal line, lithium was the **only** agent of five — against rapamycin, resveratrol, N-acetylcysteine and a superoxide dismutase mimetic — to counteract most respiratory parameters at both time points.⁶⁵ That is a favourable comparative result and is reported with the caveat that concentrations are not stated in the abstract.

And the absence. **There is no adequate demonstration of lithium-induced mitophagy in neurons.** The claim circulates widely. The primary evidence is a loss of complex IV protein after 120 hours in a kidney-derived cell line — bulk turnover, not selective mitophagy⁴⁹ — and one ultrastructural study in spheroids whose authors state outright that no molecular validation was performed, no LC3B, no PINK1 or Parkin immunoblotting, and describe the images only as "suggestive of" organelle-selective autophagy.⁶⁶ PINK1/Parkin-dependent lithium mitophagy in neurons is an unfilled gap, and given that the corpus's Phase I rests on mitophagy failure in the locus coeruleus, it is a conspicuous one.

PART THREE — THE ELEMENT ACROSS THE PHASES

VII. Phase I — The Brainstem, the Clock, and an Asymmetry Nobody Has Remarkd

Phase I of the corpus is a silent erosion beginning in the third decade: the locus coeruleus, its noradrenergic projection, the circadian and sleep machinery that defends it, and the vagal and gut afferents that load it. A substrate claim has to say what lithium does there. The honest answer is that it does a great deal to the clock, very little that anyone has measured to the locus coeruleus, and something to the raphe that is the mirror image of what it does to the locus — an asymmetry that appears to have gone unremarked for twenty-four years.

7.1 Circadian: strong, with a productive internal contradiction

The mechanism is unusually clean. GSK-3 β phosphorylates and stabilises REV-ERB α ; lithium triggers rapid proteasomal degradation of REV-ERB α and de-repression of *Bmal1*, and a lithium-insensitive REV-ERB α mutant blocks the effect.⁶⁷ That makes REV-ERB α a biological target of lithium, and REV-ERB α is a component the corpus's own coerulean-clock argument already runs on.

The magnitude is quantified genetically rather than pharmacologically, which is better. Mice heterozygous for GSK3 β free-run at 23.83 ± 0.05 hours against 23.54 ± 0.10 in wild-type littermates ($p = 0.0374$) — halving the gene dose lengthens the period by about a fifth of an hour.⁶⁸ Chronic lithium lengthens the period of locomotor rhythms and of PER2 bioluminescence in suprachiasmatic slices, lung and fibroblasts, and **also raises amplitude** in both central and peripheral clocks through increased *Per2* transcription rather than protein stabilisation.⁶⁹ In the suprachiasmatic nucleus itself, lithium lengthens the free-running period while GSK-3 protein falls and its inactive phosphorylated form rises, producing an antiphasic rhythm — and the effect is regionally specific, absent in the arcuate nucleus.⁷⁰

There is human evidence at two levels. In fibroblasts from nineteen bipolar patients and nineteen controls, baseline period was longer in cases; lithium at one millimolar raised amplitude by 36 per cent in controls and **failed to do so in cases**; and *GSK3B* genotype predicted lithium's rhythm effects specifically in the patient cells.⁷¹ And in a 1978 study of seven patients followed through full mania-depression cycles, a circadian rhythm free-ran fast in five, lithium slowed a rhythm in five, and the two patients whose clocks appeared too slow were lithium **non-responders**.⁷²

The contradiction is the useful part. A screen of 1,280 compounds found that selective small-molecule GSK-3 inhibitors and GSK-3 β silencing **shorten** the period, opposite to lithium's lengthening.⁷³ So lithium's circadian effect is not purely GSK-3-mediated, and the likely second arm is inositol: manipulating inositol hexakisphosphate and its kinases alters circadian amplitude and period, and knocking down inositol polyphosphate multikinase attenuates lithium's rhythm effects — though

lithium did not change inositol hexakisphosphate content, so simple depletion is not the mediator.⁷⁴ This is the same two-armed structure as Chapter V, in a different system, and it should be argued rather than smoothed. **Verdict: strong.**

7.2 The locus coeruleus: thin, and never actually tested

This needs to be said without decoration, because the corpus's Phase I is built on the locus coeruleus and a reader will assume the lithium literature addresses it. It does not.

A search of the entire indexed literature for lithium and the locus coeruleus returns eleven records. Six are false positives in which lithium appears only as the seizure adjuvant in lithium-pilocarpine epilepsy models or as the malaise agent in conditioned taste aversion; a seventh is a connectivity study with no lithium in it. Three survive, and only one is specific.

That one is worth the whole section. In rats fed lithium for twenty-one days to a serum concentration of 0.98 ± 0.1 millimolar, whole-brain vesicular monoamine transporter 2 messenger RNA rose 199 ± 27 per cent. Regionally, it rose 50 to 100 per cent in the raphe nuclei, the ventral tegmental area and the substantia nigra — and **fell by about 50 per cent in the locus coeruleus.**⁷⁵ Lithium moves the locus coeruleus in the opposite direction to every other monoamine nucleus in the same animal. Nobody has followed it up in twenty-four years.

The second is older and is a negative. Chronic lithium slightly enhanced Purkinje cell responsiveness to iontophoretic noradrenaline while acute lithium antagonised it — a reciprocal adaptive change — but "inhibitory responses to locus coeruleus stimulation were unaffected by chronic LiCl treatment."⁷⁶ Chronic lithium alters post-synaptic noradrenergic sensitivity without changing locus coeruleus output.

The third is a single modern paper in which conditional deletion of *ErbB4* in noradrenergic locus coeruleus neurons increases spontaneous firing through NMDA-receptor hyperfunction, raises cerebrospinal catecholamines and produces mania-like behaviour, all **completely rescued by lithium.**⁷⁷

Beyond those three there is nothing. No study of lithium on locus coeruleus neuron number, on tau in the locus coeruleus, on locus coeruleus volume or neuromelanin signal in humans, on tyrosine hydroxylase there, or in any model of noradrenergic degeneration. **Lithium has never been tested against locus coeruleus degeneration.** For a volume placing lithium in this corpus, that is the most important sentence in the chapter. **Verdict: thin.**

7.3 The raphe: strong at the terminal, explicitly null at the cell body

The serotonergic picture is unusually well resolved and it has a shape. After forty-eight hours of lithium at brain and plasma concentrations of 0.4 to 1.0 mEq L⁻¹, the response of hippocampal pyramidal neurons to iontophoretic serotonin was **unchanged**, while the effect of electrically stimulating the ascending serotonergic pathway was **doubled**, and abolished by a serotonergic neurotoxin. Unitary recording from the dorsal raphe showed lithium "changed neither the number of spontaneously active 5-HT neurons nor their mean firing rate."⁷⁸ A follow-up found terminal and somatodendritic

autoreceptor function unchanged while the response to intravenous 8-OH-DPAT doubled, implicating a subset of postsynaptic 5-HT_{1A} receptors rather than the autoreceptors.⁷⁹ Transporter autoradiography makes the anatomy explicit: chronic lithium increased serotonin transporter density in frontal, temporal and entorhinal-piriform cortex and lateral hypothalamus, and "the only modifications observed were located in regions containing nerve terminals of 5-HT neurons, while regions with cell bodies remained unaffected."⁸⁰

Verdict: strong, and specifically about terminals.

7.4 The asymmetry

Put the two sections together and something emerges that neither literature has stated.

Lithium acts on monoamine **terminal fields** — transporter density, evoked release, postsynaptic receptor sensitivity, vesicular loading — while leaving the cell bodies of origin electrophysiologically untouched. That is established twice over, in the raphe by Blier and de Montigny and at the locus coeruleus by Siggins and Schultz. And in the one experiment that examined both nuclei in the same animals, lithium raised vesicular monoamine transporter expression in the raphe, ventral tegmental area and substantia nigra while lowering it in the locus coeruleus.

So: lithium treats the locus coeruleus differently from every other monoamine nucleus, and it does so in the direction of *reduced* vesicular monoamine handling. The corpus's Phase I argues that the locus coeruleus fails first because it is uniquely loaded — long unmyelinated projections, high metabolic cost, a tonic firing pattern, and noradrenaline's own auto-oxidative chemistry. A pharmacological agent that specifically lowers vesicular monoamine transporter expression in that nucleus and nowhere else is, on the corpus's own account, doing something with a sign that is not obviously protective. Vesicular sequestration is what keeps catecholamines out of the cytosol; less of it means more cytosolic noradrenaline available for auto-oxidation.

This volume does not assert that lithium is harmful to the locus coeruleus. One paper, one species, one dose, messenger RNA rather than protein or function, and no cell-count or pathology endpoint. It asserts something narrower and more useful: that **the single most specific result linking lithium to the corpus's Phase I nucleus points in an unwelcome direction, has never been replicated, and has never been followed by a functional experiment.** Chapter XVI turns that into a named prediction with a stated falsifier. Of everything in this volume it is the cheapest thing to test and, if the sign is real, the most consequential.



VIII. Phase II — Glia, and the Contradiction in the Myelin Arm

Phase II is microglia, the inflammasome and the matrix. Lithium's glial literature is substantial, internally consistent on cytokines, and carries one genuine mechanistic conflict that a serious volume has to put at the centre rather than the margin.

8.1 GSK-3 as an innate-immune rheostat

The foundational result is not a brain paper. Stimulating human monocytes through Toll-like receptors 2, 4, 5 or 9 with GSK-3 inhibited produces a large increase in interleukin-10 with **simultaneous** suppression of interleukin-1 β , interleukin-6 and interleukin-12, and the mechanism is competition between NF- κ B p65 and CREB for the shared coactivator CBP; inhibiting GSK-3 shifts occupancy toward CREB.⁸¹ The bidirectionality is the claim: GSK-3 does not merely promote inflammation, it actively suppresses the anti-inflammatory arm. In vivo, a GSK-3 inhibitor protected mice against endotoxin shock.

The extension into glia is by analogy and was done by other groups, with lithium itself. In rat primary microglia and organotypic hippocampal slices, lithium chloride downregulated inducible nitric oxide synthase, interleukin-1 β , interleukin-6 and tumour necrosis factor α and upregulated interleukin-10 and the mannose receptor; the effects were mimicked by Wnt3a and reversed both by a canonical Wnt blocker and by a PPAR γ antagonist, so two convergent pathways.⁸² In lipopolysaccharide-activated microglial lines, lithium lowered the Notch intracellular domain dose-dependently, raised inhibitory serine-9 phosphorylation of GSK-3 β and Akt, attenuated nuclear p65, decreased interleukin-1 β , tumour necrosis factor α , interleukin-6, nitric oxide synthase, cyclo-oxygenase 2 and monocyte chemoattractant protein 1, and notably increased interleukin-10.⁸³ The same signature recurs in rat cortical glia and in vivo rat models.^{84,85} Astrocytes carry the same axis: 6-hydroxydopamine activated GSK-3 β and translocated p65, and both lithium chloride and a selective inhibitor suppressed the whole pro-inflammatory output;⁸⁶ GSK-3 inhibition also blocks the STAT3-driven transcriptional programme of reactive astrogliosis, including GFAP itself.⁸⁷

Verdict: strong on the cytokine signature, with the honest qualification that no experiment has used primary human microglia. One flat negative exists and should be cited: in cultured rat brain astrocytes and microglia, thiadiazolidinones suppressed interleukin-6, tumour necrosis factor α , nitric oxide synthase and cyclo-oxygenase 2 entirely PPAR γ -dependently, and "in contrast the glycogen synthase kinase 3beta inhibitor LiCl did not show any effect."⁸⁸

8.2 The inflammasome, and a reversal of sign

The lithium-NLRP3 literature is thinner and less tidy. In mice after middle cerebral artery occlusion, with lithium chloride at one millimole per kilogram per day producing serum around 0.8 and cerebral tissue around 0.5 millimolar — clinically realistic concentrations, which is why this paper is worth its length — NLRP3 rose **only in neurons**, with no increase detected in astrocytes or microglia, while caspase-1 and gasdermin D rose in all three. Lithium suppressed all of it, through a pathway dissected step by step: Akt to inhibitory GSK-3 β phosphorylation to β -catenin stabilisation, β -catenin with TCF4 to STAT3 to uncoupling protein 2 to reduced mitochondrial reactive oxygen species to reduced NLRP3, with a parallel Akt-FoxO3a arm, and each step abolished by its own specific inhibitor.⁸⁹

Against that, in a human microglial line stimulated with tumour necrosis factor α , interleukin- 1β and interferon γ at brain-equivalent lithium concentrations, lithium **treatment** reduced inflammasome gene expression and activity, while lithium **pretreatment significantly elevated** inflammasome activity.⁹⁰ The direction of lithium's inflammasome effect depends on its timing relative to the stimulus. Any flat statement that lithium is anti-inflammatory is therefore wrong, and the corpus should not make one.

8.3 What lithium depletion does to microglia

The depletion experiment is the most Phase-II-relevant thing in the *Nature* paper. Single-nucleus sequencing of lithium-deficient microglia overlapped significantly with the human Alzheimer microglial transcriptome, specifically with the **GPNMB-expressing** population that expands with disease progression; GPNMB itself was significantly upregulated, as was lipoprotein lipase, and CD68-immunoreactive microglial density rose in two independent amyloid models. The differentially expressed genes were enriched for Alzheimer genome-wide-association risk genes. Functionally, microglia from lithium-deficient wild-type mice released more interleukin-6, tumour necrosis factor, granulocyte colony-stimulating factor and three chemokines on stimulation, and showed **significantly reduced amyloid- β 42 uptake and degradation** — restored by two structurally distinct GSK-3 β inhibitors.⁶

GPNMB and lipoprotein lipase are genuine disease-associated-microglia module genes, so it is defensible to write that lithium depletion drives microglia toward a DAM-like, GPNMB-high, phagocytically incompetent state. It must be said in the same breath that **TREM2 itself was not tested**, and that a targeted search for lithium and TREM2, and for lithium and the DAM signature, returns nothing at all.

This is also the neatest connection in the volume to work outside it. GPNMB is the ligand by which microglia transfer functional mitochondria to astrocytes in extracellular vesicles, a transfer that alleviates pathology in tauopathy mice and whose loss worsens it. A lithium-depletion phenotype that drives GPNMB up therefore sits on a bridge between the bioenergetic and glial arms that neither literature has crossed. It is listed as a prediction in Chapter XVI.

8.4 Myelin, and the contradiction

Lithium depletion produced a myelin phenotype. Fluoromyelin labelling showed significant loss; oligodendrocytes, oligodendrocyte precursors and axons were reduced in lithium-deficient amyloid-model **and wild-type** mice, so the phenotype does not require amyloid; electron microscopy of the corpus callosum showed thinner sheaths and a significantly elevated g-ratio across 1,376 and 1,396 axons pooled from eight mice per group; hippocampal proteomics showed reduced myelin protein abundance; and a GSK-3 β inhibitor restored oligodendrocyte number and myelin basic protein expression, so the arm is kinase-dependent.⁶

And the mechanism has a direct, well-evidenced pillar. Four chemically unrelated GSK-3 β inhibitors — including lithium — increased oligodendrocyte precursors and mature oligodendrocytes and promoted myelination in vivo and in intact optic nerve, with GSK-3 β inhibition proving pro-survival and

anti-apoptotic, acting through CREB stimulation and reduced Notch1.⁹¹ Convergence across four unrelated compounds is the strongest on-target argument available.

The same paper contains the problem. Direct comparison showed that **Wnt3a and GSK-3 β inhibition have opposing actions on oligodendrocytes**: GSK-3 β inhibition markedly increased differentiation while Wnt3a inhibited it, with GSK-3 β inhibition overriding Wnt3a's negative effect. And an independent, genetic line of work establishes that the proximal consequence of GSK-3 β inhibition is bad for myelin. Dysregulated Wnt- β -catenin signalling profoundly delays both developmental myelination and remyelination, shown two ways — conditional β -catenin activation in the oligodendrocyte lineage, and haploinsufficiency for an endogenous Wnt inhibitor — with elevated Wnt transcripts found in human multiple sclerosis lesions.⁹² The therapeutic direction in that programme is the *opposite* of lithium's: stabilise Axin2 in order to **degrade** β -catenin, which accelerates precursor differentiation and myelination after hypoxic and demyelinating injury.⁹³

So lithium inhibits GSK-3 β , which stabilises β -catenin, which blocks oligodendrocyte differentiation — yet lithium promotes oligodendrocyte differentiation. The resolution offered by the people who found both halves is that GSK-3 β acts on differentiation through CREB and Notch1 as well as through Wnt, and that its inhibition overrides Wnt3a. That is a real, unresolved mechanistic conflict, and it is one of the more defensible things in this volume to interrogate rather than to report.

One distinction closes the chapter and applies to the whole of Part Three. Lithium *depletion* producing myelin loss is evidence that endogenous lithium is **required**. That is a different claim from lithium being **therapeutic**, and the two are run together constantly in this literature. The rodent remyelination evidence for lithium comes from injury models — intracerebral haemorrhage, where lithium ameliorated myelin and axonal degeneration and reduced mature oligodendrocyte death through BDNF downstream of GSK-3 β inhibition⁹⁴ — and from developmental and organotypic preparations. Searches for lithium with cuprizone and with experimental autoimmune encephalomyelitis return nothing. There is no classical demyelination model in the lithium literature at all.

8.5 The human white-matter evidence, which does not cooperate

If lithium preserved myelin in humans, the place to see it is the bipolar imaging literature, and it is equivocal. In the largest diffusion dataset assembled — 3,033 individuals across 26 cohorts — fractional anisotropy was lower in patients in 29 of 43 regions, and "lithium medication, later onset and short disease duration were related to higher FA along multiple ROIs." The case-control effect sizes are $r \approx 0.04$, and the lithium association is a cross-sectional medication-status covariate.⁹⁵ A later analysis in the same consortium found lithium-treated patients had a weaker negative association between fractional anisotropy and body mass index in two tracts — an interaction, not a main effect.⁹⁶ And the cleanest single dissociation is a well-characterised euthymic sample of sixty patients and sixty controls in which lithium was associated with bilateral temporal grey-matter increase but **not with any diffusion parameter**.⁹⁷ In children with intrauterine lithium exposure, no structural or diffusion differences were found.⁹⁸

The grey-matter literature is more favourable and still small. The only direct pooled estimate across fifteen studies and 854 patients is a standardised mean difference of **0.17 (95% CI 0.01–0.33, p = 0.035)**, significant with semi-automated segmentation and **not significant with fully automated segmentation**.⁹⁹ Meta-regressions find grey matter rising with the proportion of patients on lithium,^{100,101} and in one analysis the lithium-associated enlargement overlapped anatomically with the region where grey matter was reduced in the disease.¹⁰² Against that, a meta-analysis of first-episode mania found no moderating effect of lithium use,¹⁰³ and the largest medication-focused analysis — 2,664 patients and 4,065 controls across 34 groups — found that medication-**free** patients barely differ from controls ($d = 0.06$ – 0.07), that medicated patients show smaller subcortical volumes and larger ventricles, and that lithium's apparent benefit is an **interaction** offsetting the negative association between antiepileptic use and hippocampal volume ($\beta = 0.19$, $q = 0.038$).¹⁰⁴

The confounds are live and they are not rhetorical: illness burden, responder selection in cohorts recruited from lithium clinics, concomitant medication, and mood state at scan. The volume's summary is that the direction is consistent across four independent meta-analyses, the magnitude is small, part of it may be methodological, and none of it is randomised or longitudinal.

IX. Phase III — The Brake Reelin Was Already Pulling

This chapter contains the volume's principal novel proposal. It is graded **speculative**, and the grading is the point: what follows is an argument that a specific experiment has never been done, not a claim about what its result would be.

9.1 The cascade, which is not in doubt

Reelin binds the ectodomains of the very-low-density-lipoprotein receptor and apolipoprotein E receptor 2 directly; blocking those receptors abolishes reelin-induced tyrosine phosphorylation of the adaptor Dab1; and **mice lacking either reelin or both receptors show hyperphosphorylation of tau**.¹⁰⁵ Double knockouts of the two receptors precisely phenocopy the reeler and Dab1-null mice.¹⁰⁶

The step that matters here is the next one. Reelin binding stimulates phosphoinositide 3-kinase, which activates protein kinase B, which **inhibits glycogen synthase kinase-3 β** — genetically dependent on both receptors and on Dab1, with the signalling components enriched in axonal growth cones.¹⁰⁷ The physical link is Dab1 binding the p85 α regulatory subunit of the kinase, Src-family-dependent and impaired by membrane cholesterol depletion.¹⁰⁸

And the kinase activity has been measured in vivo, with an apolipoprotein E gene-dose effect. In reelin-deficient mice GSK-3 β activity is increased, and increased **further** in mice deficient in both reelin and apolipoprotein E, with tau phosphorylation tracking apolipoprotein E dose; Dab1-deficient mice show increased GSK-3 β and also increased CDK-5. Phosphatase activity was unchanged in every condition, so this is a kinase effect rather than a phosphatase effect.¹⁰⁹ That paper names the reelin–apolipoprotein-E-receptor–Dab1 complex as a tau-phosphorylation brake.

One limiting result belongs here for accuracy: phosphoinositide 3-kinase and Akt are required for cortical plate organisation but **GSK-3 β is not** the effector for that particular function, where mTOR mediates dendritic growth instead.¹¹⁰ Reelin's GSK-3 β arm is real and is not the arm that does lamination — which is precisely what frees it to be the arm that does tau.

9.2 Where the corpus already stands

This corpus has built a substantial part of Phase III on reelin. It carries the COLBOS variant and the pharmacological question of whether a drug can copy the luckiest mutation; it carries the architect's handshake, the architect's scaffold and the architect's reprieve; it has already corrected itself once on the chemistry, resolving one sulfated lattice into two polymers and establishing that reelin's obligate co-receptor is heparan rather than chondroitin sulfate. It treats the reelin brake on tau as a load-bearing claim.

So the corpus holds that a brake on GSK-3 β fails in Phase III, and it holds — from the metallome chapter of this volume — that an element whose depletion raises GSK-3 β expression and activation is itself depleted in the same brains. Those are two failures of restraint on the same kinase, described in two literatures, in one disease.

9.3 The gap, stated exactly

A search of the entire indexed literature for reelin together with lithium returns **five records**. Not one is a mechanistic study.

The most relevant is a screen: rat prefrontal cortex under chronic psychotropics including lithium, with quantitative polymerase chain reaction and immunoblot for reelin, the very-low-density-lipoprotein receptor, Dab1, GSK-3 β and glutamic acid decarboxylase. Reelin, Dab1 and GSK-3 β were each significantly altered by multiple drugs at both messenger RNA and protein level.¹¹¹ It is a six-drug screen, not a lithium-reelin experiment, and it reports no tau. A second finds reelin among nine genes regulated by valproate and lithium challenge in a human neuroblastoma line.¹¹² A third is a pathway analysis across roughly seven thousand subjects in which, of eighteen lithium-related molecular pathways tested, three survived permutation — **reelin, integrins and aurora**, all microtubule-related.¹¹³ The fifth is a false positive from an epilepsy model.

The fourth is the interesting one. In 2006, a review proposed exactly this argument: that failure of reelin signal transduction leading to tau hyperphosphorylation is a convergence point for Alzheimer's disease, frontotemporal dementia and schizophrenia, and it named **the lithium ion** as acting at the kinase step.¹¹⁴ It proposed the link. It did not test it. And in the twenty years since, nobody has.

Adjacent work shows the arm is therapeutically live in adult injured brain: in a mouse stroke model, an E3 ligase degrades histone deacetylase 2, raising reelin expression, which drives inhibitory serine-9 phosphorylation of GSK-3 β and is neuroprotective.¹¹⁵ No lithium in it.

9.4 The proposal

The question nobody has asked is whether **lithium substitutes for failed reelin signalling at the shared node**.

The logic is a convergence, not an identity. Reelin restrains GSK-3 β from outside the cell, through a receptor, an adaptor, a lipid kinase and a serine kinase, terminating in inhibitory phosphorylation at serine 9. Endogenous lithium status, on the evidence of Chapter II, sets the abundance and activation state of the same kinase by an unidentified route, with the inhibitory serine-9 to total ratio falling when lithium is withdrawn. Both restraints are reported to fail in Alzheimer's disease. They converge on one enzyme, and they are independent of each other: reelin's arm is receptor-mediated and extracellular, lithium's is neither.

Three consequences follow, and each is testable.

First, they should be non-additive. If both restraints terminate on the same kinase, then a brain with an intact reelin arm has less to gain from lithium repletion than a brain whose reelin arm has failed — and conversely, lithium repletion should matter most where reelin signalling is already compromised. That predicts an **interaction**, not a main effect, and it predicts the direction. The corpus already holds two human populations in which the reelin arm differs by genotype: apolipoprotein E4 carriers, in whom the reelin brake is weakened and in whom reelin-deficient mice show the gene-dose effect on tau phosphorylation described above; and the COLBOS reelin variant carriers, in whom it is strengthened. A lithium effect that is real and that runs through this node should be larger in the first group and smaller in the second.

Second, it makes the corpus's own knife-edge sharper. The corpus has already identified that heparin, heparinase and NDST1 knockout are simultaneously the tools used to block tau uptake and the manipulations that abolish reelin signalling — a collision between two literatures that do not cite each other. If lithium restrains the same kinase reelin restrains, then lithium is the first candidate in that argument that acts on the brake **without touching the sugar**. That is a genuinely useful property and it belongs in the therapeutic-landscape reasoning.

Third, it predicts a specific negative. If lithium's benefit ran through this node, then in a system where reelin signalling is intact and maximal, lithium should do nothing. That is exactly the shape of the result in Chapter VI, where lithium had no bioenergetic effect whatever on healthy neurons and a dose-dependent effect on diseased ones; and of the result in Chapter V, where its clearance arm is use-dependent by enzyme kinetics. A restraint that only matters when another restraint has failed is the signature of a substrate, and it is why this volume argues for a Groundwork placement rather than a phase.

9.5 What would refute it

The proposal fails if any of the following holds. Lithium repletion rescues tau phosphorylation in reelin-null or Dab1-null mice **to the same degree** as in wild-type — which would show the two arms are independent rather than convergent, and would remove the interaction the proposal rests on. Or: the serine-9 phosphorylation change under lithium depletion proves to be a consequence of raised total

kinase rather than a regulated change in phosphorylation state, in which case the node the two arms supposedly share is not shared at all. Or: the apolipoprotein E4 interaction runs the wrong way in the existing trial data, which is checkable now, at no cost, in the Forlenza cohort and in the LATTICE amyloid subgroup if genotype was collected.

Chapter XVI states these as numbered falsifiers. The claim is entered in the ledger at the weakest available tier, because a convergence argument built on one unmeasured premise is a conjecture, and the corpus has been burned before by exactly this shape of inference — the first-ember argument required a third, unmeasured premise about sulfation and was demoted for it.



X. The Matrix

The seventh axis is the corpus's claim that extracellular matrix and perineuronal net integrity is a dimension of collapse in its own right. The expectation going into this chapter was that lithium would have nothing to do with it. That turned out to be wrong, and the connection is not through the kinase.

A direct lithium-sensitive enzyme sets chondroitin sulfation. BPNT2 is a Golgi bisphosphate nucleotidase directly inhibited by lithium, metabolising the by-products of glycosaminoglycan sulfation. Nervous-system-specific knockout decreased total glycosaminoglycan sulfation across brain regions and specifically **decreased chondroitin-4-sulfate with a compensatory increase in chondroitin-6-sulfate** in cerebral cortex and hippocampus.²⁴ The 4-sulfate to 6-sulfate ratio is the parameter that governs how strongly a net restricts plasticity — high 4-sulfate is restrictive, and the developmental shift toward it is what closes critical periods.

The authors are scrupulous that these changes did **not** produce gross alterations in perineuronal nets and that neurobehavioural assays were unremarkable. So the finding is not that lithium remodels nets. It is that lithium has a characterised, direct, family-member target that sets the sulfation code of the matrix in the hippocampus, and that nobody has asked what that does in a disease where the net is being degraded.

The kinase arm reaches the net too, in one paper. Overexpressing GSK-3 β in adult-born dentate granule cells altered gephyrin cluster number and size, increased inhibitory currents, shortened and displaced the axon initial segment, reduced synaptic output to CA3 and CA2, impaired pattern separation — **and triggered depletion of parvalbumin-interneuron perineuronal nets.**¹¹⁶ A kinase whose activity rises when lithium falls depletes the nets the corpus places at the centre of the Phase II to Phase III transition.

And lithium partially rescues net and parvalbumin loss in one model. In a developmental ethanol model, parvalbumin-positive cell density in barrel cortex fell 25 per cent by postnatal day 90 with no reduction at day 14 — a maturation failure rather than acute death — and in exposed adults more than

twenty per cent of net-positive cells lacked parvalbumin, where in controls net-positive cells were virtually all parvalbumin-positive. Lithium given on the day of exposure, or delayed to days 14 to 28, attenuated the parvalbumin loss.¹¹⁷ A companion paper in the same model reported that a single injection of lithium chloride on the day of exposure reduced adult hyperactivity, cognitive impairment, the reduction in slow-wave sleep, and the decrease in parvalbumin and net density in retrosplenial cortex and dorsal CA3.¹¹⁸

Beyond those three there is nothing. No study of lithium on aggrecan, brevican, tenascin-R or lectican proteolysis in the adult or aged brain; no lithium with chondroitinase; no lithium and perineuronal nets in any Alzheimer or tauopathy model. **Verdict: thin, but not empty — and the BPNT2 mechanism is the most under-exploited single fact in this volume.**



XI. Trophic Subsidy, Neurogenesis, and the Senescent Clock

Three shorter axes, one of which carries the best-evidenced result in the entire volume.

11.1 BDNF: the necessity test exists

Lithium raises cellular brain-derived neurotrophic factor content by three days and TrkB tyrosine-490 phosphorylation by five days in cortical neurons. Both a Trk inhibitor and a BDNF-neutralising antibody abolish lithium's neuroprotection. And decisively: **lithium fails to protect cortical neurons from homozygous and heterozygous BDNF-knockout mice while fully protecting wild-type littermates.**¹¹⁹ BDNF is not a correlate of lithium's action. It is required, and the requirement is gene-dose sensitive.

The transcriptional mechanism is worked out. Therapeutic lithium selectively raises exon IV-containing BDNF messenger RNA and promoter IV activity; the effect is mimicked by pharmacological GSK-3 inhibition and by silencing GSK-3 α or GSK-3 β ; and the lithium-responsive element sits **upstream of the calcium-responsive elements**, with deletion of all three failing to abolish activation.¹²⁰ That is a calcium-independent route into BDNF, distinct from the activity-dependent one.

For a corpus that runs a withdrawn-trophic-subsidy argument — that the synapse fails when its trophic support is withdrawn, and that exercise prevents but does not cure — this is the cleanest available pharmacological entry point, and it comes with a genetic necessity test that almost nothing else in this volume has. **Verdict: strong.**

11.2 Adult neurogenesis: strong in rodent, absent in human tissue

Chronic lithium increases dentate gyrus proliferation by 25 per cent in mouse by three-dimensional stereology, with about 65 per cent of new cells co-labelling for a neuronal marker,¹²¹ and by 54 per cent at

twelve hours and 40 per cent at twenty-eight days in rat, with about 90 per cent neuronal.¹²² That second study contains a caution worth keeping: long-term potentiation was enhanced but **independently of the neurogenesis**, tracking CaMKII, phospho-Elk, TrkB and phospho-CREB instead, and two days of lithium enhanced potentiation with no neurogenesis at all. Do not conflate the two.

The mechanism is Wnt- β -catenin, with a full behavioural rescue: in the Ts65Dn model of Down syndrome, chronic lithium promoted precursor proliferation through pharmacological activation of that pathway, restored dentate neurogenesis to physiological levels, fully rescued the synaptic plasticity of newborn granule neurons, and restored fear conditioning, object location and novel object recognition.¹²³ And the genetic proof that the inhibitory serine site is the node: knock-in mice in which GSK-3 α and β cannot be inhibitorily phosphorylated show a 40 per cent impairment of dentate neurogenesis, and chronic lithium plus fluoxetine increases precursor proliferation in wild-type but **not** in the knock-in.¹²⁴

The human case, however, rests entirely on imaging. In 342 controls and two matched groups of 51 psychotic bipolar patients, lithium-free patients had significantly reduced right hippocampal subfield volumes and thinner occipital cortex against controls while **lithium-treated patients differed from controls in neither**.¹²⁵ Searching for lithium with doublecortin in human post-mortem hippocampus returns **zero records**. There is no human histological evidence that lithium increases adult neurogenesis, and volumetry and spectroscopy cannot distinguish neurogenesis from neuropil, glia or water.

That matters more now than it did a year ago, because the corpus's own grading of human adult neurogenesis is out of date: a multiomic study of 355,997 nuclei across young, aged, superager, preclinical and Alzheimer hippocampi identified neural stem cells, neuroblasts and immature granule neurons, with dysregulation largely chromatin-driven and already detectable in preclinical disease. Two ledger rows in this corpus still read *contested*. They should be regraded, and this volume's neurogenesis claims are written against the new grading rather than the old.

11.3 Senescence and the telomere

In 131 bipolar patients and 336 controls, patients **never treated with lithium** had shorter leukocyte telomeres than controls ($p = 0.029$), patients with a lithium history had longer telomeres than never-treated patients ($p = 0.015$) and did not differ from controls — and Mendelian randomisation showed no association between the disorder and genetically determined telomere length, so the shortening is acquired rather than inherited.¹²⁶

The mechanistic counterpart is better than usual and includes human tissue. GSK-3 β is overexpressed and hyperactive with age in glomerular podocytes; podocyte-specific ablation attenuates senescence and organ ageing in mice; **p16^{INK4A} and p53 contain high numbers of GSK-3 β consensus motifs, physically interact with the kinase and behave as substrates**; microdose lithium late in life reduced senescence signalling and delayed ageing in mice; and in humans, lithium carbonate therapy inhibited GSK-3 β and mitigated senescence signalling in urinary exfoliated podocytes with preserved kidney function.¹²⁷ It is not neural tissue, and that is stated — but it is direct human evidence that therapeutic lithium suppresses p16 and p53 senescence signalling in vivo, and the substrate relationship transfers.

The necessary counterweight is that lithium can **induce** senescence. In primary human articular chondrocytes, lithium-mediated GSK-3 β inactivation increased mitochondrial reactive oxygen species, arrested cells in S phase, and produced a full DNA-damage-response phenotype: γ H2AX, GADD45 β , p21, senescence-associated β -galactosidase, 8-oxo-deoxyguanosine, increased cell size and granularity.¹²⁸ The direction of effect is cell-type dependent, and lithium should not be described as uniformly senostatic. It does, for what it is worth, sit in the top tier of the geroprotective canon alongside rapamycin, senolytics, metformin, acarbose, spermidine and the NAD⁺ enhancers.¹²⁹

11.4 Parvalbumin and gamma — and a sign problem

The corpus's Phase III therapeutic reasoning leans on restoring gamma. The only direct work on lithium and gamma is two papers from one laboratory in the pedunculopontine nucleus — brainstem, so Phase I territory. Neuronal calcium sensor 1, overexpressed in some post-mortem bipolar brain, enhances inositol trisphosphate receptor activity and **increases** gamma oscillation amplitude; lithium **decreases** gamma frequency and amplitude by downregulating calcium channel activity through G-protein over-inhibition of P/Q-type currents, at 10 micromolar within five minutes.^{130,131}

The authors frame this as normalisation: given the overexpression, lithium restores gamma toward baseline. That is a fair reading of their system. It is also the opposite sign from what a "restore gamma in Alzheimer's disease" argument wants, and the corpus should state the tension rather than smooth it — particularly since the gap scan that prompted this volume identified an independent internal contradiction in the same Phase III therapeutic pairing. There is no study of lithium on cortical or hippocampal gamma power in vivo, in rodents or humans, and none on lithium and parvalbumin interneurons in any Alzheimer, tau or amyloid model.

PART FOUR — THE HUMAN RECORD

XII. The Trials, the Registries, and the Water

The mechanistic chapters are the interesting part of this volume. This one is the part that decides whether any of it matters to a patient, and it is where a corpus that prides itself on grading its own claims has to be most careful, because the human record is thinner and more contradictory than the enthusiasm around it.

12.1 The randomised trials, in order

Trial	Design	n	Dose / level	Result
Hampson 2009	Single-blind, PC, 10 wk, mild AD	71	0.5–0.8 mmol L ^{−1}	Co-primaries not met. No effect on lymphocyte GSK-3 activity or any CSF biomarker; ADAS-Cog p = .11
Forsythe 2011	Double-blind, PC, 12 mo, aMCI	45	0.25–0.5 mmol L ^{−1}	CSF P-tau ↓ (p = .03); better ADAS-Cog and attention
Forsythe 2019	Same cohort, 2 yr DB + 2 yr SB	61	0.25–0.5 mEq L ^{−1}	Placebo declined, lithium stable; CSF Aβ42 ↑ at 36 mo
Neufeld 2013	Microdose, 15 mo, AD	<i>not stated</i>	300 µg day ^{−1}	No MMSE decline vs declining controls

Trial	Design	n	Dose / level	Result
De va na nd 20 21 (L it- A D)	Double-blind, PC, 12 wk, agitation	77	150–600 mg day ⁻¹	Primary not met; serum BDNF unchanged
Gi ld en ge rs 20 26 (L A T TI CE)	Double-blind, PC, 2 yr, MCI	80	mean 195 mg day ⁻¹ , serum 0.17 mEq L ⁻¹	None of six co-primaries met

Four observations about that table matter more than any single row.

The positive signal is one cohort, not three trials. Forlenza 2011 and Forlenza 2019 are the same study, grown from 45 to 61 participants, and the 2023 naturalistic follow-up is the same cohort again. Reviews and meta-analyses routinely treat them as independent. The 2011 report gives a p-value of 0.03 for one cerebrospinal biomarker among several, with **no effect size, no confidence interval and no adjustment for multiplicity**; the other two biomarkers were unchanged. The 2019 report gives no effect sizes, no confidence intervals and no p-values at all, and does not state conversion rates despite listing conversion as a secondary outcome. The thirteen-year follow-up reports a Cohen's d of 1.78 on verbal fluency from 22 former lithium and 14 former placebo participants, after 41 per cent attrition with differential mortality.^{132–134} That effect size is larger than anything ever seen in a randomised comparison of anything in this disease, and it should be read as what attrition does, not as what lithium does.

The microdose trial cannot carry the weight placed on it. Nunes 2013 does heavy lifting in the "microdose works" argument. Its abstract does not state the sample size, the randomisation or blinding procedure, the serum levels achieved, or any p-value, effect size or confidence interval, and the paper is not in the open archive.¹³⁵ This volume does not quote an n for it and does not count it as evidence.

The best-designed modern trial is negative. LATTICE randomised 83 and treated 80 for two years, with a prespecified α of 0.01 across six co-primary outcomes. None was met.¹³⁶ The near-signal was verbal memory — 0.69 points per year, 95% CI 0.005 to 1.37, p = .05 — against underlying decline of 1.42

points per year on placebo and 0.73 on lithium. Hippocampal volume $p = .09$; cortical grey matter $p = .78$; the global composite $p = .80$; visual memory $p = .78$; BDNF $p = .93$. A seventh planned outcome, GSK-3 activity, could not be assessed because the assays failed quality control.

The meta-analytic record has flipped. The 2015 meta-analysis everyone cites found a standardised mean difference of -0.41 (95% CI -0.81 to -0.02 , $p = 0.04$) across three trials and 199 participants for the cognitive analysis, with **no significant difference in any cerebrospinal biomarker**.¹³⁷ The most recent, PROSPERO-registered with frequentist and Bayesian analysis and trial sequential analysis, covers six trials and 394 participants and concludes that "current evidence does not support consistent cognitive or functional benefits in AD dementia" — global cognition on the Mini-Mental State Examination a mean difference of -1.61 (95% CI -4.11 to 0.88), not significant.¹³⁸ A 2026 systematic review adds the observation that should trouble any broad neuroprotection claim: across four randomised trials in bipolar disorder, lithium showed **no consistent cognitive improvement or worsening**.¹³⁹ If lithium were generally neuroprotective, decades of patients on therapeutic concentrations ought to show a cognitive benefit, and in randomised comparisons they do not.

There are two honest defences of LATTICE and both should be stated. It achieved a mean serum level of 0.17 mEq L^{-1} , well below the Forlenza target, and its own authors conclude that older adults tolerate more than 300 mg per day poorly and that future trials should use 150 to 300 mg. And only 21 of 75 participants who underwent amyloid imaging were amyloid-positive, so an anti-amyloid-pathway mechanism was largely tested in people without the pathology. In the amyloid-positive completers the exploratory effect sizes were Hedges' g of 0.74 for verbal memory and 0.81–0.82 for hippocampal volume, against 0.09–0.32 in the amyloid-negative — which is the single result the "right drug, wrong patients" argument rests on, and it comes from about twenty-one people. It used lithium carbonate, which Chapter XIII shows is the salt the sequestration hypothesis predicts will fail.

12.2 The registries, and the study that removes the bias

The observational literature is usually summarised as showing that lithium-treated patients get less dementia. The primary result of the study that started it says the opposite.

In Denmark from 1995 to 2005, 16,238 people who purchased lithium at least once were compared with a 30 per cent random population sample of 1,487,177. **People who had ever purchased lithium had an increased rate of dementia: RR 1.47 (95% CI 1.22–1.76).**¹⁴⁰ The protective claim comes from a within-exposed analysis: among those who *continued* lithium, the rate fell to population level after roughly one prescription and stayed there. That is a comparison between people who stayed on a drug and people who stopped it — healthy-adherer bias and reverse causation, since incipient dementia is itself a reason to discontinue. The author says methodological explanations cannot be excluded. A dissertation reporting only "lithium protects" is misreporting the source.

The subsequent studies divide along exactly the lines that bias predicts. A bipolar cohort found the rate falling after the second prescription with no equivalent effect for anticonvulsants, antidepressants or antipsychotics.¹⁴¹ A United States claims analysis found a hazard ratio of 0.77 (95% CI 0.60–0.99) in the longest exposure stratum and **null results at 61–300 and 1–60 days**.¹⁴² A United Kingdom

secondary-care cohort found dementia at 0.56 (95% CI 0.40–0.78) — from 548 exposed patients and 53 events, with protection apparent at **under one year** of exposure, which is biologically implausible for a disease-modifying mechanism and is better read as a bias signal.¹⁴³ A 2026 propensity-matched network analysis reports a hazard ratio of 0.48 from 34 and 69 events in cohorts of 67,020 each, an Alzheimer incidence of under 0.1 per cent in adults over fifty with mood disorders, which signals severe under-ascertainment.¹⁴⁴

And then the study that matters. Using the entire Danish population, with an active comparator and sustained exposure defined over consecutive six-month periods across ten years of follow-up, in cohorts of 12,607 and 156,678, **there was no systematic statistically significant difference between sustained lithium and sustained lamotrigine or valproate for any physical disorder including dementia** — the single exception being myxoedema, which the authors attribute to detection bias from routine thyroid monitoring.¹⁴⁵ The author of the 2008, 2010 and 2017 positive studies, using the design built to remove healthy-adherer bias and confounding by indication, found the dementia effect disappear.

This is the strongest single argument against the epidemiological case and it belongs in any honest treatment.

12.3 The water, and its shape

Six studies have asked whether lithium in drinking water tracks dementia. The exposure range is wide enough to make the question reasonable: across 369 samples from 21 United States utilities, groundwater ran 0.9 to 161 $\mu\text{g L}^{-1}$ with a median of 13.9, surface water below 0.5 to 130 with a median of 3.9, conventional treatment does not remove lithium, and 56 per cent of groundwater samples exceeded the non-regulatory health-based screening level.¹⁴⁶

The flagship study is a Danish nationwide nested case-control of 73,731 dementia cases and 733,653 matched controls, with a kriging-interpolated exposure model accounting for residential moves — the most sophisticated exposure estimation in this literature. Cases had a median of 11.5 $\mu\text{g L}^{-1}$ and controls 12.2. And the dose-response is **explicitly non-linear**. Against a reference of 2.0–5.0 $\mu\text{g L}^{-1}$: above 15.0 $\mu\text{g L}^{-1}$ the incidence rate ratio was 0.83 (95% CI 0.81–0.85); at 10.1–15.0 it was 0.98 and not significant; and at **5.1–10.0 it was 1.22 (95% CI 1.19–1.25) — more dementia, not less.**¹⁴⁷

That shape is not what a pharmacological effect looks like. It is what geographic confounding looks like, and the authors say as much: confounding from factors associated with municipality of residence cannot be excluded. It matters for this volume specifically because the *Nature* paper's discussion describes this study as showing "a significant inverse correlation" between water lithium and dementia incidence.⁶ That is a simplification of a U-shaped, ecologically confounded association, and it is the one place where the paper's framing overreaches its cited support.

Nor does it replicate. In Texas, change in age-adjusted Alzheimer mortality correlated negatively with trace lithium at $r = -0.20$ — about four per cent of variance — and significance survived adjustment for gender, race, education, rural living and air pollution but **not** adjustment for physical inactivity, obesity

or type 2 diabetes, which were themselves negatively correlated with water lithium.¹⁴⁸ Lithium-rich counties are metabolically healthier counties. In Japan, across 808 cities, an inverse association appeared in **females only**, not in males and not in the total population.¹⁴⁹ In Scotland, across 37,597 people and 3,605 incident dementias at concentrations an order of magnitude below Denmark's, lithium was **positively** associated with dementia in women — highest in the second quartile at HR 1.17 (95% CI 1.04–1.32) — and unassociated in men, and the authors concluded their results do not support an association.¹⁵⁰ A United States groundwater analysis lost its association after adjustment for county demographics and healthcare resources.¹⁵¹ And the newest and largest, using the entire Medicare population of about 62 million, reports a prevalence ratio of 0.965 and an incidence rate ratio of 0.958 — a 3.5 and 4.2 per cent difference — with mortality among people with dementia *higher* in high-lithium counties, an association that largely dissolved on stratification by a single demographic variable.¹⁵²

The pro-lithium systematic review of this literature concedes the structure of the problem in its own tabulation: four of five studies found an association when they controlled for nothing; after adjustment, one held in both sexes, one in females only, and two lost it entirely — and **age categories were not controlled in any of the five**.¹⁵³ Its own limitations section names the geology confound.

The volume's conclusion on the water literature is therefore unambiguous. Every study is ecological or semi-ecological; none measures individual intake, diet, bottled water or supplements; lithium in groundwater is set by bedrock geology, which co-varies with urbanisation, water hardness, agriculture, industry and deprivation; the dose-response is non-monotonic in the largest study; the association vanishes under adjustment in two; it reverses direction in women in the cohort with the most cases; and in the largest dataset ever assembled the effect is three to four per cent. This literature cannot support a causal claim, and citing it as though it could is the most common error made about lithium and dementia.



XIII. The Salt Question

The sequestration hypothesis has a therapeutic corollary that is cleaner than anything else in the paper and more contested than anything else in the volume: that the right salt is one amyloid does not adsorb.

13.1 The claim

Reasoning that an electrostatic lithium–amyloid interaction should scale with a salt's ionisation, the authors measured the conductivity of sixteen lithium salts and found inorganic salts — including the clinical standard, carbonate — significantly more conductive than organic ones ($p = 8 \times 10^{-4}$). Lithium orotate had the lowest conductance across the whole range and was taken forward.⁶

The pharmacological result is load-bearing. After seven days at $4.3 \mu\text{Eq L}^{-1}$ in drinking water — about 30 μg of elemental lithium per litre — serum and hippocampal lithium **did not differ** between the orotate

and carbonate groups. But laser-ablation mapping showed lithium highly concentrated in plaques after carbonate and much less so after orotate, and **orotate, but not carbonate, significantly elevated lithium in the non-plaque parenchymal fraction**. Same total brain lithium; different bioavailable brain lithium.

The efficacy differential follows. Treated from five to twelve months, orotate at the physiological dose almost completely prevented plaque deposition and phospho-tau accumulation while carbonate and a sodium orotate anion control had no significant effect. Treated from nine to eighteen months, against established pathology, orotate significantly reduced plaque burden and tangle-like density while carbonate did not — though the vehicle group in that experiment was $n = 3$. In aged J20 mice treated from seventeen to twenty-two months, orotate reduced plaque burden by about **70 per cent**, the only percentage efficacy figure in the paper. Orotate but not carbonate raised PSD-95 and myelin basic protein, increased oligodendrocyte number and suppressed gliosis; orotate at the *lowest* dose almost completely reversed memory loss where carbonate and the anion control did not. In normal ageing wild-type mice from twelve to twenty-four months it largely prevented age-related gliosis, restored aged microglial amyloid degradation, prevented spine loss and largely reversed water-maze and novel-object decline. Long-term dosing did not alter blood urea nitrogen, creatinine or thyroid-stimulating hormone.

A supporting behavioural study reports a roughly tenfold potency difference — near-complete block of amphetamine-induced hyperlocomotion at 1.5 mg kg^{-1} orotate against partial block at $15\text{--}20 \text{ mg kg}^{-1}$ carbonate — with organic anion transport inhibitors blocking orotate's effect while sparing carbonate's, and with carbonate but not orotate causing polydipsia, raised creatinine in males and raised thyroid-stimulating hormone in females.¹⁵⁴

13.2 The critique

In June 2026 a three-author correspondence in the *British Journal of Psychiatry* argued that the salt claim "requires further scrutiny" on four grounds: no study has demonstrated the presence of stable lithium orotate in physiological fluids; acid–base chemistry predicts it is largely protonated in the stomach, so it dissociates and is absorbed as free lithium ion; experimental studies indicate the two salts have comparable oral pharmacokinetics; and lithium carbonate is also neuroprotective, including at very low doses. Their conclusion is that disproportionate focus on a specific salt "could have safety implications and may distract from answering fundamental questions about the effects of very low doses of lithium."¹⁵⁵

Two things about the provenance make this harder to dismiss than a routine objection. The second author is a retired analytical chemist, so the chemistry is not amateur. And the first author is also senior author of the pro-lithium systematic review of the water literature and of a review of lithium's grey-matter effects. He is not a lithium sceptic. He is a lithium advocate objecting specifically to the salt.

The critique reaches further than the therapy. The sequestration mechanism explains why bioavailability falls further in Alzheimer's disease than in mild cognitive impairment, and it explains the differential rescue by supposing the **counter-ion** governs amyloid binding after administration. If orotate dissociates on absorption, there is no amyloid-evading lithium salt, the differential rescue needs

another explanation, and the strongest defence against LATTICE — wrong salt — disappears.

13.3 What pharmacokinetic data actually exist

Almost none. There is no human head-to-head comparison of the two salts.

What exists is a single case report in which an eighteen-year-old ingested eighteen 120-milligram lithium orotate tablets and reached a serum lithium of 0.31 mEq L^{-1} at ninety minutes and 0.40 an hour later, with mild nausea and tremor resolving in three hours; that paper states explicitly that "prior human and animal data have shown similar pharmacokinetics and shared clinical effects of these lithium salts."¹⁵⁶ A second case report describes a woman taking internet-purchased orotate whose serum lithium was **below 0.05 mmol L^{-1}** — a supplement dose producing essentially undetectable serum lithium.¹⁵⁷ Nine healthy men given 5 mg per day of lithium orotate for up to twenty-eight days produced a detectable brain lithium magnetic resonance signal, broadly stable between day fourteen and day twenty-eight, with two subjects two- to four-fold higher than the rest; adherence was self-reported and the spatial resolution coarse.¹⁵⁸ That study's stated purpose was to build a method that would "permit the comparison of different lithium salt preparations." **The comparison has not been done.**

The historical human base for orotate efficacy is one uncontrolled private-practice series from 1986: forty-two alcoholic patients on 150 mg per day for at least six months, drawn from 105 who started — a 60 per cent discontinuation within six months — with calcium orotate, magnesium orotate, bromelain and phospholipids co-administered.¹⁵⁹

Meanwhile an unregulated market exists. In a survey of 211 adults taking over-the-counter lithium, the most common preparation was aspartate at 10 mg once daily, the most commonly perceived benefit was cognition, and "side effects and withdrawal phenomena were more prevalent than anticipated."¹⁶⁰

The volume's position: the claim that orotate reaches brain parenchyma better than carbonate rests on one mouse and post-mortem study, one mouse potency study, and a worthless 1986 case series. The counter-case is chemical, pharmacokinetic and empirical. **Any proposal to give anyone lithium orotate for prevention has to say this first**, and a corpus that publishes a therapeutic landscape has an obligation to say it plainly.



XIV. The Ceiling

Any prophylaxis argument in this disease runs into a constraint the mechanistic chapters can ignore and a clinician cannot. Lithium has a narrow therapeutic index, and the organ risks are quantified.

The definitive synthesis screened 5,988 abstracts and included 385 studies.¹⁶¹ Glomerular filtration rate fell by 6.22 mL min^{-1} , **not significant**. Urinary concentrating ability fell by about 15 per cent of maximum — a weighted mean difference of $-158.43 \text{ mOsm kg}^{-1}$ (95% CI -229.78 to -87.07 , $p < .0001$).

Renal replacement therapy occurred in 18 of 3,369 patients, 0.5 per cent. Clinical hypothyroidism carried an odds ratio of **5.78 (95% CI 2.00–16.67)**. Blood calcium rose 0.09 mmol L^{-1} and parathyroid hormone 7.32 pg mL^{-1} . There was **no significant increase in congenital malformations** in the pooled analysis. The authors' conclusion is measured: little evidence of clinically significant renal impairment in most patients, low risk of end-stage failure, and a recommendation that calcium be checked before and during treatment because of the consistent hyperparathyroidism signal.

Modern cohort data sharpen it and — critically for this volume — supply a threshold. In a Hong Kong population cohort of 7,029 patients followed a mean 8.3 years against non-lithium mood stabilisers, hypothyroidism ran at an adjusted hazard ratio of 2.00 (95% CI 1.72–2.33) and chronic kidney disease stage 3 or worse at 1.35 (95% CI 1.15–1.60), while **stage 4 and end-stage disease were not increased**. The serum thresholds derived by Youden index were **above 0.50 mEq L^{-1} for thyroid dysfunction and above 0.59 for renal**.¹⁶² A cohort of 1,012 lithium-treated patients found chronic kidney disease incidence of about 1.2 per cent per exposed patient-year, stage 4 at 0.0004 per patient-year, and **no cases of end-stage renal disease**.¹⁶³ Against that, Australian registry data record 187 people commencing renal replacement therapy with lithium-induced nephropathy over twenty years, with incidence rising 5.6-fold from 0.14 to 0.78 cases per million per year — a rare absolute event, and the most alarming credible datapoint in the literature.¹⁶⁴

Hyperparathyroidism deserves its own line because it is routinely missed. Pooled prevalence of lithium-associated hypercalcaemia is 3.17 per cent by total calcium and 4.23 per cent by ionised calcium; hyperparathyroidism runs at about 4 per cent against 0.5 per cent in the healthy population, an eightfold increase; and **51 per cent of cases are multiglandular**, which matters surgically. The authors note calcium and parathyroid hormone are insufficiently measured in practice.¹⁶⁵

Teratogenicity has been revised downward and the revision is dose-dependent. Across 1,325,563 pregnancies with 663 first-trimester lithium exposures and lamotrigine as an active comparator, cardiac malformations occurred in 2.41 per cent of exposed against 1.15 per cent unexposed, an adjusted relative risk of 1.65 (95% CI 1.02–2.68). The dose-response is the part that matters: **at $600 \text{ mg per day or less}$, RR 1.11 (95% CI 0.46–2.64)**; at 601–900 mg, 1.60; above 900 mg, **3.22 (95% CI 1.47–7.02)**. Right ventricular outflow tract obstruction — the Ebstein category — ran 0.60 against 0.18 per cent, adjusted RR 2.66 with a lower confidence bound of exactly 1.00. The authors' own sentence is that "the magnitude of this effect was smaller than had been previously postulated."¹⁶⁶

14.1 The one number that makes a prophylaxis argument arguable

The thyroid and renal risk thresholds sit at roughly 0.50 to 0.59 mEq L^{-1} . LATTICE achieved a mean of **0.17**. The Forlenza trials targeted 0.25 to 0.50. The dose range in which the low-dose hypothesis operates is therefore **below the concentrations at which the two principal organ toxicities become detectable**, and below the dose at which teratogenic risk becomes significant.

That is the strongest structural argument for a low-dose prophylaxis trial, and it should be stated as a constraint satisfied rather than a benefit demonstrated. LATTICE remains the best modern safety dataset at these concentrations and it is not reassuring in the way advocates suggest: serious adverse events in 29

per cent of the lithium arm against 23 per cent of placebo, none judged definitely related; the one death was in the placebo group; but diarrhoea, tiredness and tremor all ran roughly double placebo, and 36 per cent of participants discontinued.¹³⁶ The authors' operational conclusion — that older adults tolerate more than 300 mg per day poorly — is the single most practically useful sentence in the clinical literature.

The mouse safety data, for what they are worth, showed no change in blood urea nitrogen, creatinine or thyroid-stimulating hormone on long-term low-dose orotate. No histological renal endpoint was reported, and it is a mouse.

PART FIVE — THE CASE AGAINST, AND WHAT WOULD SETTLE IT

XV. The Case Against

A volume that argues for a new substrate node has an obligation to state the strongest honest case against it, ranked by how much damage each objection actually does, and to say for each what evidence would answer it. Eleven objections follow. Three do real damage. Four are serious. Four are caveats that are commonly mistaken for refutations. None is individually fatal, and taken together the first four mean the causal claim is **unestablished rather than refuted** — which is a different thing, and the difference is the whole position of this volume.

15.1 There is no independent replication

Thirteen months after publication, no independent group has reproduced the human measurement. No matters-arising, correction or replication is indexed. The only peer-reviewed correspondence engaging the paper substantively is the critique of the salt claim in Chapter XIII. And the concession is available from the friendliest possible source: a narrative review by the authors of the original grey-matter finding, among lithium's most prominent champions, states in its own abstract that "the recent repletion hypothesis suggests that lithium may also function as a physiological trace element, **but these findings await independent replication.**"¹⁶⁷

Internal replication is not the same thing and the distinction should be exact. The paper replicates three ways — a second brain-bank cohort, sixty cases run by a different laboratory, forty-eight cases by an alternative digestion protocol. That is good practice and it largely answers contamination. But all three used tissue from the same donor pool, selected and shipped by the same investigators. They replicate the **measurement**, not the **observation**. An independent replication needs a different brain bank, different case selection and different hands.

Severity: serious; fatal if it persists. What would answer it: an independent group measuring cortical lithium in control, MCI and Alzheimer tissue from a non-overlapping cohort, pre-registered, with cause of death, renal function, body-mass trajectory and medication history in the model.

15.2 The mechanism does not survive a concentration calculation

Set out in full in Chapter II and conceded in the source paper. Endogenous cortical lithium is three to four orders of magnitude below its inhibition constant at GSK-3 β ; the depletion that produces pathology changes direct occupancy by under a hundredth of one per cent. The magnesium-competition correction is directionally right and quantitatively unspecified.

The logical residue is the part that matters and it is worth restating because it is easy to elide. The paper's positive mechanistic evidence is that GSK-3 β expression and activation rise under depletion, and that two structurally unrelated GSK-3 β inhibitors reverse the phenotype. A rescue by inhibition of an enzyme

establishes that the enzyme **sits downstream of the lesion**. It does not establish that the enzyme is lithium's target. Note also that one of the two rescue agents is a potent Wnt- β -catenin activator rather than a clean kinase probe.

Severity: serious. It kills the mechanism as stated, not the phenomenon. What would answer it: genetic epistasis — a GSK-3 β conditional knockout or kinase-dead knock-in rendered lithium-deficient. If the phenotype persists, the mechanism is wrong. And, separately, measurement of free intracellular lithium activity rather than total tissue content.

15.3 Reverse causation cannot be excluded by this design

The human arm is cross-sectional, post-mortem and matched only for age and sex. Four specific pathways, each with support.

Diet. Accelerated weight loss *precedes* the diagnosis of Alzheimer-type dementia by years — the rate roughly doubles about a year before diagnosis, and future converters weigh less at enrolment while still cognitively normal.¹⁶⁸ In imaging cohorts, cognitively normal people losing five per cent of body weight have higher baseline tau and amyloid measures, thinner cortex and faster atrophy.¹⁶⁹ Dietary lithium comes overwhelmingly from grains, vegetables and water, so a hypophagic prodromal population is a lithium-underconsuming population by construction. The partial rebuttal is real — serum lithium did not differ between groups — but the serum samples are the most recent available from an unspecified and variable interval before death, temporally mismatched from post-mortem cortex, and serum lithium is set by renal handling, which is itself disturbed in late dementia.

Barrier. Blood-brain barrier and pericyte injury appear in the hippocampus in early cognitive dysfunction independently of amyloid and tau status.¹⁷⁰ Lithium crosses by transport rather than free diffusion; a damaged barrier is a plausible route to altered partitioning as a consequence of degeneration. Barrier function is not addressed in the paper.

Composition. The dry-to-wet ratio check is a real control and it forecloses the crude version of this objection. It does not foreclose the refined one: Alzheimer cortex loses neurons, synapses and myelin and gains glia, and if lithium partitions preferentially into a compartment that shrinks, per-gram concentration falls with no change in availability to surviving cells. Reporting per unit wet weight makes the measure a composite of concentration and cytoarchitecture.

Agonal state. Post-mortem interval was checked and had no effect, which is fair — but it is the weakest of the post-mortem confounders. Tissue pH and agonal duration dominate; in prefrontal cortex, pH correlates with over 35,000 messenger RNA variants against 99 for post-mortem interval.¹⁷¹ Neither pH nor agonal duration is reported, and people dying with end-stage dementia differ systematically in terminal hypoxia, dehydration and renal impairment — the states that shift monovalent cation distribution.

A fifth point applies specifically to the group carrying the temporal argument. A post-mortem mild-cognitive-impairment group consists of people **who died while still in MCI** — a survivorship-selected set who died of something else before converting, typically with higher competing

mortality and mixed pathology. It is not a snapshot of people on the way to Alzheimer's disease.

Severity: serious, and irreducible in this design. It kills "upstream in humans," which is the volume's actual claim. It does not touch the mouse arm, which is causally independent: reverse causation does not explain why removing lithium from a mouse's diet raises amyloid and phospho-tau. What would answer it: longitudinal lithium measurement in living people with serial biomarker imaging — or, cheaply and immediately, re-analysis of the existing cohort data adjusting for body-mass slope, cause of death, estimated glomerular filtration rate, agonal duration and tissue pH.

15.4 The two arms do not connect quantitatively

This is the objection this volume considers most under-appreciated, and it can be made entirely from the paper's own reported ranges.

Control-diet mice carried cortical lithium of 1.61–4.59 ng g⁻¹. Cognitively normal humans carried 0.52–6.0 ng g⁻¹. Depleted mice fell about half, to roughly 0.8–2.3 ng g⁻¹.

A substantial fraction of the cognitively normal human controls sits at or below the cortical lithium concentration that is pathogenic in the depleted mouse. If about 2 ng g⁻¹ of cortex were sufficient to drive amyloid deposition, tau phosphorylation, demyelination and memory loss, a large share of the control group should be affected, and they are not — they are the controls. A threshold-deficiency model does not fit the human distribution the paper itself reports. Either mice are far more lithium-dependent than humans, or per-gram cortical content is not the relevant variable.

Three further problems attach to the depletion arm. Logically, a deprivation phenotype demonstrates that an organism **requires** a substance; it says nothing about whether ordinary variation in that substance causes disease. Iodine deprivation causes cretinism, which does not make iodine deficiency a cause of goitre in Iowa. Second, the readouts come substantially from aggressive transgenic overexpression models whose record of predicting human outcomes is poor; the ageing wild-type arm is the more interesting data and its effects are more modest — elevated amyloid- β 42 with only a trend for amyloid- β 40. Third, rodent renal lithium clearance, dietary density per kilogram and brain-to-plasma ratios are not shown to be human-equivalent; overlapping steady-state concentrations do not establish equivalent flux or sensitivity.

Severity: serious. It kills the quantitative bridge between the two arms. What would answer it: a graded dose-response holding mice across the *observed human range* — say 3.5 down to 2.4 ng g⁻¹ — rather than 100 per cent down to 50. If pathology appears only below the human range, the human difference is not pathogenic.

15.5 The prior from failed metal interventions

Set out in Chapter 4.3. Twenty-two years, three programmes, and one that accelerated decline in the patients who received it while demonstrably engaging its target. This does not falsify the lithium hypothesis — the direction is opposite and the preclinical package is stronger — but it establishes the prior, and it establishes that **confirmed target engagement is not evidence of benefit. Severity:**

serious as a prior. Answered only by a randomised trial.

15.6 The supporting epidemiology is non-monotonic and partly null

Chapter 12.3. **Severity: serious. It removes support rather than providing counter-evidence.** What would answer it: an individual-level exposure study, or a Mendelian randomisation design using variants in lithium handling. No such study exists; that is an absence, not evidence.

15.7 The best modern trial was negative

Chapter 12.1, with its two legitimate defences — under-dosing at 0.17 mEq L^{-1} and a largely amyloid-negative population — and the observation that the defence rests on a subgroup of about twenty-one people. **Severity: serious. It does not refute the hypothesis; it means the therapeutic corollary is currently unsupported.**

15.8 The orotate claim may not describe a real chemical entity

Chapter XIII. **Severity: serious for the therapy, moderate for the mechanism,** because it removes the counter-ion explanation for differential rescue and with it the strongest defence against the negative trial.

15.9 Selective GSK-3 inhibitors failed

Chapter 3.4, with the two readings and the three caveats. **Severity: caveat as evidence, serious as an argument.** It undercuts the mechanistic story considerably and does not undercut the existence of the phenomenon. What would answer it: a brain-penetrant selective inhibitor, dosed to confirmed central target engagement, in amyloid-positive prodromal disease. If that fails, the kinase mechanism is dead regardless of lithium.

15.10 The effect size sits inside the between-cohort variance

The analytics deserve credit and this volume gives it in Chapter 1.3; a critique leading with contamination will be dismissed. The objection that survives is about scale rather than technique. The values are single-digit nanograms per gram with standard deviations around half the mean, and the paper's **own two cognitively normal groups differ by about 48 per cent** in mean cortical lithium — 2.36 against 3.50 ng g^{-1} . A gap between two sets of healthy people that is plausibly as large as the disease difference. Statistical significance is not in doubt at these sample sizes; a significant difference in a measure whose healthy-population variance exceeds the effect is nonetheless a weak biological signal, and per-gram wet weight is the wrong denominator for a bioavailability claim. **Severity: caveat.** What would answer it: absolute effect sizes with confidence intervals alongside p-values, normalisation to total protein or to a co-measured metal with no disease association, and quantification of free rather than total lithium.

15.11 Lithium's essentiality is asserted more than demonstrated — and the paper does not need it

The strongest essentiality case reviews rat and goat low-lithium ration studies showing higher mortality and reproductive and behavioural abnormalities, and proposes a provisional intake of 1,000 µg per day for a seventy-kilogram adult.¹⁷² Note what its own advocate concedes in the same abstract: "in humans defined lithium deficiency diseases have not been characterized." The supporting human evidence is ecological, of the design class that failed in objection 6. The best modern review restates that "this element is not officially considered to be a micronutrient."¹⁷³ The nutritional framework classifies lithium among elements with at most an apparent beneficial intake, explicitly declining to assign a recommended intake on the grounds that the words *adequate* and *safe* would mislead.¹⁷⁴

There is no lithium recommended intake, no recognised human deficiency syndrome, and **no identified lithium-dependent enzyme, transporter or binding protein**. For a genuinely essential element that last absence is remarkable: we know the proteins that make iodine, selenium, zinc and molybdenum essential.

Severity: caveat — and a trap in both directions. The argument does not require lithium to be a classical essential nutrient. It requires only that endogenous brain lithium have a physiological function, which the depletion experiment supports. Presenting this work as establishing an essential micronutrient with a deficiency disease overreaches and inherits the whole weak essentiality literature as a liability; attacking essentiality as though it were the claim is a straw man. The two should be kept separate.

15.12 A note on what the sceptic must concede

Six things, because a chapter that only attacks is not useful and a volume that omits them reads as motivated.

The human measurement is blinded, technically careful, internally replicated across two cohorts, two laboratories and two digestion protocols, with published recoveries, detection limits and duplicate reproducibility. Lithium was the only metal of twenty-seven significantly reduced in both mild cognitive impairment and Alzheimer's disease and carried the lowest adjusted p-value of any metal, so multiple comparisons were handled and it won on merit. The **regional dissociation is a genuine internal control** — reduced in affected prefrontal cortex, not reduced in relatively spared cerebellum — and a generic agonal, nutritional or barrier artefact should not respect Braak topography; the counter-argument is available but narrow, since regional atrophy and regional barrier injury respect that topography too. The depletion arm is causally independent of the human arm, prospective, and converges across three model systems and multiple readouts from electron-microscopic g-ratio to microglial transcriptome to behaviour. The transcriptomic overlap with human disease was a non-obvious prediction that could have failed and did not. And lithium in the surviving parenchyma correlated with antemortem episodic memory, semantic memory and global cognition across the whole ageing population — a dose-response-like relationship inside the human data.

15.13 The sentence this volume defends

Aron and colleagues establish that endogenous lithium has a physiological function in the mouse brain and that cortical lithium is reliably lower in human mild cognitive impairment and Alzheimer's disease. They do not establish that this difference is causal, upstream, or of a magnitude that matters in humans; the proposed GSK-3 β mechanism is inconsistent by three to four orders of magnitude with lithium's known pharmacology; and as of September 2026 no independent group has reproduced the human measurement.



XVI. What Would Settle It

Fourteen experiments, ordered by what they would decide rather than by cost. The first four are the ones that matter; the rest are cheap, and several can be done on data that already exist.

1. Independent replication of the human measurement. A non-overlapping brain bank, pre-registered, with cause of death, estimated glomerular filtration rate, body-mass trajectory, agonal duration and tissue pH in the model. *Refutes if cortical lithium does not differ by diagnosis in an independent cohort.* This is the gate. Nothing downstream is worth much until it is passed.

2. Graded depletion across the human range. Hold mice at cortical lithium concentrations spanning the observed human control-to-disease range rather than 100 to 50 per cent. *Refutes the causal claim if pathology appears only below the range human controls occupy.*

3. Genetic epistasis on the kinase. Lithium depletion in a GSK-3 β conditional knockout or kinase-dead knock-in. *Refutes the published mechanism if the depletion phenotype persists without the kinase.*

4. Free versus total lithium. Any method that measures lithium ion activity rather than total tissue content, in control and disease tissue. *Reframes everything if the free fraction does not track the total.*

5. The reelin interaction — the volume's own prediction. Lithium repletion in reelin-null, Dab1-null and receptor-double-null mice against wild-type, with tau phosphorylation as the readout. The proposal in Chapter IX predicts **sub-additivity**: less rescue where the reelin arm is already absent, because both restraints terminate on the same kinase. *Refuted by equal rescue in null and wild-type.*

6. The apolipoprotein E interaction, testable today at no cost. If the convergence in Chapter IX holds, lithium's effect should be larger in apolipoprotein E4 carriers, in whom the reelin brake is weakened. Genotype data very likely exist in the Forlenza cohort and in the LATTICE participants. *Refuted if the interaction is absent or runs the other way.*

7. The locus coeruleus vesicular transporter result. Replicate the single 2002 finding that lithium lowers vesicular monoamine transporter 2 expression in the locus coeruleus while raising it in every other monoamine nucleus, at protein and functional level, and pair it with a cell-count and tau endpoint in an ageing model. *This is the cheapest consequential experiment in the volume.* If the sign is real and functional, a prophylaxis proposal aimed at Phase I has a problem at the exact nucleus Phase I is about.

8. The v-ATPase liability in neurons. Test directly whether lithium interferes with the vacuolar ATPase and impairs lysosomal acidification in neurons at achievable concentrations, as it does in CD8⁺ T cells. *If it does, the clearance argument inverts.*

9. Lithium on the proteasome, in neurons, at achievable concentrations, with a ubiquitin-reporter readout — closing the control the original autophagy work did not run.

10. A head-to-head pharmacokinetic comparison of orotate and carbonate in humans, with speciation analysis demonstrating whether an intact lithium-orotate complex exists in plasma and brain. The ⁷Li imaging method built for exactly this comparison already exists and has not been used for it.

11. Isolation of the autophagic arm in vivo. Knock down inositol monophosphatase in a tauopathy mouse to separate the inositol arm from the kinase arm genetically rather than pharmacologically. No such experiment has been done.

12. Mitophagy, properly. PINK1/Parkin-dependent mitophagy under lithium in neurons, with molecular validation rather than electron micrographs.

13. The BPNT2-matrix link. Whether lithium at achievable concentrations shifts the chondroitin 4-sulfate to 6-sulfate ratio in adult hippocampus, and whether that changes perineuronal net integrity in a tauopathy model.

14. Mendelian randomisation on variants in lithium transport and handling against dementia risk. This would be the first non-ecological test of the environmental-exposure claim, and it has never been attempted.

16.1 Falsifiers of this volume's own placement

The substrate claim advanced in Chapter XVII fails if: cortical lithium does not differ by diagnosis in an independent cohort (experiment 1); or the depletion phenotype is reproduced only at concentrations below the human control range (experiment 2); or the phenotype survives loss of GSK-3 β and no alternative lithium-sensitive node can be identified, in which case the mechanism is unfalsifiable rather than merely unknown; or lithium proves to impair lysosomal acidification in neurons at achievable concentrations (experiment 8), which would place it against the corpus's central mechanism rather than with it.

XVII. Where It Sits

The question this volume was written to answer is not whether lithium is a treatment. It is where an element belongs in an architecture.

17.1 Not a phase

Lithium is not a phase of the disease and should not be given one. It has no onset, no anatomy of its own and no temporal signature. Its concentration in human cortex is largely unchanged with age.⁸ What it has is a distribution — heterogeneous across fourteen brain regions, highest in the caudate, lowest in brainstem and cerebellum, and unlike sodium and rubidium, which are homogeneous. Something regional governs it, and nobody knows what: the paper that establishes endogenous lithium is "dynamically regulated in the brain" identifies **no transporter, demonstrates no regulated uptake or efflux, and measures no set-point**. That is a real gap in the account and it is stated as one.

17.2 A Groundwork substrate

The corpus's Groundwork shelf holds the physiology the disease exploits rather than the disease itself: the rule by which a neuron earns the right to stay connected, the ion that carries the signal and the bill, the organelle that pays it, the lipid the brain is built from. Lithium belongs there, and the case is structural rather than enthusiastic.

It satisfies the three tests the shelf implies. It is **present in every brain and required in the mouse**: near-total dietary removal produces amyloid, phospho-tau, microglial activation and loss of synapses, axons and myelin, in wild-type animals as well as transgenic ones — so the phenotype does not require a disease model to appear. It is **upstream of more than one phase**: its depletion phenotype touches microglia and myelin (Phase II) and synapses (Phase III) simultaneously rather than sequentially, with amyloid and phospho-tau both already elevated at five weeks. And it is **use-dependent**, which is what distinguishes a substrate from a driver — its enzyme family is inhibited uncompetitively with respect to substrate, so inhibition scales with flux; its mitochondrial effect appears only in diseased neurons and not at all in healthy ones; and its clearance arm acts on soluble and pre-tangle species while the mature deposit sits outside the machinery entirely.

That last property is the one worth dwelling on, because it is the same shape three times over, arrived at from three independent literatures. A substrate is not something whose absence causes a disease. It is something whose adequacy determines how much insult a system absorbs before it fails — and the signature of such a thing is that supplementing it does nothing to a healthy system and something to a compromised one. Lithium shows that signature in bioenergetics, in enzyme kinetics and, if the Chapter IX proposal survives its falsifiers, in its relation to the reelin brake.

17.3 What it changes in the existing architecture

Three revisions, graded.

The plaque acquires a category. The corpus's vocabulary for the deposit is *marker*, *consequence*, *tombstone*. Sequestration adds **sequestrant**: a lesion that is harmful without being toxic, by removing a scarce beneficial element from the tissue around it. This is the single most consequential amendment in the volume and it is a friendly one — a tombstone made of blotting paper is still a tombstone. Graded **moderate**, because the same mechanism makes part of the lithium deficit downstream of amyloid, which cuts against the framing the source paper puts on it.

Phase I acquires a liability rather than an intervention. The volume went looking for lithium as a Phase-I-matched prophylaxis, which is what the gap scan that prompted it suggested, and found instead that lithium has never been tested against locus coeruleus degeneration at all, and that the one specific result linking it to that nucleus points in an unwelcome direction. The circadian joint is strong and the raphe joint is strong; the coerulean joint is thin and its sign is unexamined. A corpus whose Phase I is the locus coeruleus should record that as it stands. Graded **weak**, one study, one species, messenger RNA only.

Phase III acquires an unremarked convergence. Reelin restrains GSK-3 β through Dab1, phosphoinositide 3-kinase and Akt; endogenous lithium status sets the same kinase's abundance and activation; both restraints fail in the disease; the intersection has five records in the entire literature and no mechanistic study; and a 2006 review proposed exactly this and was dropped. Graded **speculative**, with five numbered falsifiers and one interaction test that can be run today on genotype data that probably already exist.

17.4 What it does not change

The therapeutic landscape. Nothing in this volume supports recommending lithium, in any salt, at any dose, to anyone for the prevention of dementia. The best-designed modern trial missed all six of its co-primary endpoints; the most recent meta-analysis of six trials and 394 participants is negative; the one epidemiological design built to remove healthy-adherer bias found no effect across 156,678 patients; the water literature is ecological, non-monotonic and vanishes under adjustment in two of six studies; the salt on which the mouse efficacy depends may not exist as a distinct species in vivo; and an unregulated supplement market is already operating ahead of all of it, with users reporting side effects and withdrawal more often than anticipated.

The corpus should say that plainly and in the same breath as the mechanism, because the mechanism is genuinely interesting and the gap between an interesting mechanism and a recommendation is exactly where this field has done its worst damage. Deferiprone hit its target and made patients worse.

17.5 The honest summary

Endogenous lithium has a physiological function in the mammalian brain. Cortical lithium is reliably lower in human mild cognitive impairment and Alzheimer's disease, by a measurement that is technically excellent, internally replicated three ways, and independently unreplicated. Part of that deficit is produced by the amyloid that adsorbs it, which makes it progressive and partly downstream. Whatever lithium does at nanomolar concentrations, it does not do by occupying an active site, and the proximal target is unidentified. Its pharmacology is a family of partially inhibited enzymes rather than a mechanism, and two of its arms oppose each other on the corpus's own central bottleneck. Its effects appear where systems have already failed and not where they have not. And the therapeutic corollary is unproven, currently unsupported, and being marketed anyway.

That is a substrate. It is not a cure, and this volume's contribution is to have said which of the two the evidence supports.

THE VALIDITY LEDGER

Every claim this volume makes that could be wrong, graded, with the experiment that would settle it. Tiers follow corpus convention: **established** — textbook, not in dispute; **strong** — well-supported primary evidence, multiple lines; **moderate** — supported but with a material gap or single-source; **weak** — inference, prediction or single unreplicated result; **contested** — the literature genuinely disagrees.

Of 78 claims: 12 established, 30 strong, 16 moderate, 13 weak, 7 contested. 42 carry a named settling experiment.

#	Tier	Claim	Basis / why	What would settle it
1	established	Zinc, copper and iron are enriched in amyloid plaques	Micro-PIXE and successors since 1998; reproduced as positive controls in the lithium mapping study	—
2	established	Micro-PIXE cannot detect lithium	Physical limit of the method below sodium	—
3	established	Endogenous human cortical lithium is $\sim 2\text{--}4\text{ ng g}^{-1}$	Two independent datasets, ICP-MS and flame AES	—
4	established	Therapeutic serum lithium is $\sim 1,000\times$ endogenous	Arithmetic from measured values; the source paper's own phrasing	—
5	established	Lithium's K_m at GSK-3 β is $\sim 2\text{ mM}$	Klein & Melton 1996, primary enzymology	—
6	established	Lithium's IC_{50} at IMPase is 0.8 mM	Hallcher & Sherman 1980, primary enzymology	—
7	established	Lithium inhibits GSK-3 by competing with magnesium, not ATP	Ryves & Harwood 2001/2002	—
8	established	Reelin binds VLDLR and ApoER2 and induces Dab1 phosphorylation	Hiesberger 1999; Trommsdorff 1999	—
9	established	Reelin signalling inhibits GSK-3 β via PI3K/Akt	Beffert 2002; Bock 2003	—
10	established	Lithium has a narrow therapeutic index with quantified thyroid, renal and parathyroid risk	McKnight 2012, 385 studies	—
11	established	Lithium reduces urinary concentrating ability by $\sim 15\%$ of maximum	McKnight 2012, WMD -158 mOsm kg^{-1}	—

#	Tier	Claim	Basis / why	What would settle it
12	established	Lithium teratogenic risk is dose-dependent and not significant at ≤ 600 mg day ⁻¹	Paterno 2017, 1.3 million pregnancies	—
13	strong	Lithium was the only metal of 27 reduced in both MCI and AD prefrontal cortex	Blinded ICP-MS, n up to 348, lowest adjusted p of any metal, three internal replications	Independent cohort measurement
14	strong	The reduction is regional — prefrontal yes, cerebellum no	Internal control in the same study	Independent cohort with the same regional contrast
15	strong	Serum lithium is not reduced in MCI or AD	Same study, n = 141/62/101	Independent replication
16	strong	Lithium is concentrated in amyloid plaques in every MCI and AD case examined	LA-ICP-MS with matrix-matched standards; Fe/Cu/Zn positive controls	Independent mapping
17	strong	Lithium binds amyloid fibrils and oligomers saturably, with a high-affinity range spanning physiological concentrations	Equilibrium dialysis	Independent binding study
18	strong	Dietary lithium removal produces AD-type pathology in mice, including in wild-type animals	92% depletion; amyloid, p-tau, synapse, axon, myelin, microglia, behaviour; two transgenic lines plus ageing WT	Graded dose-response within the human range
19	strong	Lithium depletion raises GSK-3 β expression and activating pTyr216, and lowers the pSer9:total ratio	Immunohistochemistry, proteomics and qPCR in the same study	Independent replication
20	strong	Two structurally unrelated GSK-3 β inhibitors reverse the depletion phenotype	CHIR99021 in vivo; PF-04802367 ex vivo	—
21	strong	Lithium induces autophagy by inhibiting IMPase, independently of mTOR	Sarkar 2005: IMPase inhibitor reproduces, GSK-3 inhibitor does not, mTOR readouts measured, inositol rescue	—
22	strong	GSK-3 β inhibition attenuates autophagy by activating mTOR — opposite to the IMPase arm	Sarkar 2008, with a combination-therapy proof of principle	—
23	strong	Tau is a substrate of lithium-induced autophagy in vivo	Shimada 2012: LC3 puncta up, p62 down, tangles down, motor improvement	—
24	strong	Tangle-bearing neurons are LC3-negative while LC3 puncta contain phospho-tau	Direct morphology, Shimada 2012	—
25	strong	Lithium raises respiratory chain complex activity in human brain tissue, peaking at 1 mM	Maurer 2009, human post-mortem cortex, I+III 165%, II+III 146%	—

#	Tier	Claim	Basis / why	What would settle it
26	strong	Lithium's bioenergetic effect appears only in diseased neurons	Albensi 2026: no effect on any parameter in wild-type neurons	Independent replication in human neurons
27	strong	Lithium desensitises brain mitochondria to calcium and antagonises the permeability transition, independently of GSK-3 β	Shalbuyeva 2007, with occlusion controls and a GSK-3 inhibitor negative	—
28	strong	Lithium's neuroprotection requires BDNF, gene-dose dependently	Hashimoto 2002: fails in homozygous and heterozygous knockouts, protects littermates	—
29	strong	Lithium raises BDNF via promoter IV, GSK-3-dependently and calcium-independently	Yasuda 2009, with siRNA against both isoforms	—
30	strong	Lithium lengthens circadian period and raises amplitude, via REV-ERB α /GSK-3 β	Yin 2006 mechanism; mouse in vivo and in vitro; human fibroblasts; GSK3 β heterozygote period 23.83 vs 23.54 h	—
31	strong	Lithium acts on serotonergic terminals while leaving raphe firing unchanged	Blier 1985/1987 electrophysiology; Carli 1997 transporter autoradiography	—
32	strong	GSK-3 inhibition reciprocally raises IL-10 and suppresses IL-1 β , IL-6 and IL-12	Martin 2005 mechanism via CBP competition; reproduced with lithium in four glial preparations	Primary human microglia
33	strong	Lithium depletion drives microglia toward a GPNMB-high, phagocytically incompetent state	snRNA-seq overlap with human AD GPNMB ⁺ microglia; reduced A β 42 uptake and degradation	Independent replication; TREM2 endpoint
34	strong	Selective GSK-3 inhibition failed clinically in AD and PSP	ARGO n = 306 and TAUIROS n = 146, both fully negative; adequately powered for a large effect	—
35	strong	Lithium increases rodent dentate gyrus proliferation	+25% mouse stereology, +40–54% rat, ~90% neuronal	—
36	strong	The pro-neurogenic effect requires the GSK-3 inhibitory serine site	Eom & Jope 2009 knock-in: 40% deficit, no lithium response	—
37	strong	The best-designed modern trial of low-dose lithium in MCI missed all six co-primary endpoints	LATTICE, n = 80, 2 years, prespecified α = 0.01	A trial at adequate dose in an amyloid-positive population
38	strong	The most recent meta-analysis of lithium in AD is negative	6 RCTs, 394 participants, PROSPERO-registered, frequentist and Bayesian	—

#	Tier	Claim	Basis / why	What would settle it
39	strong	A target-trial emulation across 156,678 patients found no dementia benefit for lithium over other mood stabilisers	Kessing 2024, active comparator, sustained exposure, 10-year follow-up	—
40	strong	Drinking-water lithium and dementia show a non-monotonic association in the largest study	Kessing 2017: IRR 1.22 at 5.1–10 $\mu\text{g L}^{-1}$, 0.83 above 15	Individual-level exposure study
41	strong	Thyroid and renal risk thresholds sit at ~ 0.50 – 0.59 mEq L^{-1} , above low-dose trial exposures	Chan 2025, Youden-derived thresholds, $n = 7,029$	—
42	strong	No independent group has replicated the human lithium measurement	Exhaustive search; conceded in a pro-lithium review's own abstract	Independent replication
43	moderate	Lithium's absence from the AD metallome is over-determined by instrument floor, imaging modality, conceptual frame and contamination control	Documented across four method literatures; partly inferential	—
44	moderate	Endogenous brain lithium is regionally governed by something	Heterogeneous across 14 regions unlike Na and Rb; cortex:serum ratio varies and falls in disease	Identification of a transporter or regulated flux
45	moderate	The plaque acts as a sink for a scarce beneficial element — a sequestrant, not a toxin	Four independent lines: mapping, subfractionation, mouse temporal ordering, in vitro binding	Whether raising parenchymal lithium without lowering plaque burden improves outcome
46	moderate	Lithium is a partial, parallel inhibitor of a structurally defined phosphomonoesterase family rather than a selective agent	Shared fold and ion-competition across five members; therapeutic brain levels sub- IC_{50} for all	—
47	moderate	GSK-3 maintains tau phosphorylation at PHF-1 sites but not the KXGS microtubule-binding sites	Xie 1998 epitope dissociation	—
48	moderate	Lithium's therapeutic-range tau benefit may run through ubiquitination rather than kinase inhibition	Nakashima 2005, explicit	Isolating the two arms genetically in a tauopathy mouse
49	moderate	Lithium's clinical signals come from sub-therapeutic concentrations over years, not therapeutic concentrations over months	Pattern across Hampel, Forlenza, LATTICE	—

#	Tier	Claim	Basis / why	What would settle it
50	moderate	A substantial fraction of cognitively normal humans sit at or below the cortical lithium concentration that is pathogenic in depleted mice	Arithmetic from the paper's own reported ranges	Graded depletion across the human range
51	moderate	Lithium's effect on GSK-3 in vivo is substantially indirect and protein-complex-mediated	Beaulieu 2008 β -arrestin-2 knockout genetic dissociation; Zhang 2003 autoregulation	—
52	moderate	Lithium inhibits BPNT2 and thereby sets chondroitin 4-/6-sulfation in cortex and hippocampus	Direct enzymology plus nervous-system-specific knockout; nets unchanged and behaviour unremarkable	Whether lithium shifts the 4S:6S ratio in adult hippocampus at achievable concentrations
53	moderate	Lithium partially rescues parvalbumin and perineuronal net loss in a developmental insult model	Saito 2019 and Lewin 2017, one model, one laboratory	Replication in an ageing or tauopathy model
54	moderate	Lithium arrests telomere shortening in bipolar cohorts	n = 131 vs 336 with a Mendelian randomisation control on the genetic question	Prospective measurement
55	moderate	GSK-3 β is a senostatic target with p16 and p53 as substrates, and lithium engages it in human tissue	Fang 2022: consensus motifs, physical interaction, human podocyte data	Neural tissue
56	moderate	Lithium associates with greater grey-matter volume in bipolar disorder	Four meta-analyses agree on direction; pooled SMD 0.17 (95% CI 0.01–0.33)	A randomised longitudinal imaging trial
57	moderate	The positive lithium signal in AD rests on one cohort, not three trials	Forlenza 2011, 2019 and Damiano 2023 are the same participants	—
58	moderate	Lithium orotate's differential efficacy depends on the counter-ion governing amyloid binding	Conductivity series, LA-ICP-MS differential, differential rescue — all mouse	Speciation analysis in plasma and brain; head-to-head human PK
59	weak	Endogenous lithium status sets GSK-3 β abundance and activation by an unidentified proximal target	Required by the arithmetic; no candidate identified	Identification of a nanomolar-sensitive lithium target
60	weak	Lithium expands lysosomal capacity via GSK-3 inhibition and TFEB	Inference: Parr 2012 used selective inhibitors and siRNA, not lithium	Lithium on TFEB translocation in neurons
61	weak	Lithium's two arms act at different levels of one pathway — formation versus lysosomal supply	Synthesis of Sarkar 2008 and Parr 2012; not tested as such	Simultaneous flux and lysosomal-capacity readouts under lithium

#	Tier	Claim	Basis / why	What would settle it
62	weak	Lithium shifts proteostatic burden from proteasome to autophagy rather than enhancing proteostasis	Holtz 2003 proteasome inactivation, non-neuronal, 10 mM	Ubiquitin-reporter readout under lithium in neurons
63	weak	Lithium may impair lysosomal acidification via the v-ATPase in neurons	Ma 2024 mechanism in CD8 ⁺ T cells; never tested in neurons	Direct test in neurons at achievable concentrations
64	weak	Lithium lowers vesicular monoamine transporter 2 expression in the locus coeruleus while raising it elsewhere	One study, 2002, rat, mRNA only, never replicated	Replication at protein and functional level with a cell-count endpoint
65	weak	Lithium acts on monoamine terminal fields while sparing the cell bodies of origin	Consistent across three independent studies in two nuclei; never stated as a general claim	A systematic terminal-versus-soma comparison
66	weak	Lithium substitutes for failed reelin signalling at GSK-3 β	The volume's own proposal; the cascade is established, the intersection is empty	Lithium repletion in reelin-null and Dab1-null mice against wild-type
67	weak	Lithium's effect should be larger in APOE4 carriers	Follows from claim 66 plus the Ohkubo gene-dose result	Interaction analysis in existing trial genotype data
68	weak	Lithium repletion and the reelin brake should be sub-additive	Follows from claim 66	Equal rescue in null and wild-type refutes it
69	weak	There is no adequate demonstration of lithium-induced mitophagy in neurons	Exhaustive search; the two supporting items are bulk turnover and an unvalidated ultrastructural study	PINK1/Parkin-dependent assay with molecular validation
70	weak	Lithium has never been tested against locus coeruleus degeneration	Exhaustive search: 11 records, 3 usable, none designed for the question	Any such experiment
71	weak	A 5 mg day ⁻¹ orotate dose produces a detectable human brain lithium signal	n = 9, self-reported adherence, coarse resolution, a probable units error in the report	Replication with validated adherence
72	contested	Whether the lithium deficit is causally upstream in human disease	Cross-sectional post-mortem design; the paper's own sequestration mechanism makes part of it downstream	Longitudinal lithium with serial biomarker imaging
73	contested	Whether lithium lowers amyloid via GSK-3	Phiel 2003 in <i>Nature</i> ; rebutted in <i>Nature</i> 2011 across five in vivo models; no amyloid effect in 3xTg	—
74	contested	Whether lithium's circadian effect is GSK-3-mediated	Selective GSK-3 inhibitors shorten period while lithium lengthens it	Isolating the inositol arm genetically

#	Tier	Claim	Basis / why	What would settle it
75	contested	Whether GSK-3 β inhibition helps or harms oligodendrocyte differentiation	Four inhibitors promote it; β -catenin stabilisation genetically blocks myelination	Conditional β -catenin manipulation under lithium
76	contested	Whether lithium is anti-inflammatory	Direction reverses with timing relative to stimulus in human microglia	Timing-resolved dosing studies
77	contested	Whether lithium orotate exists as a distinct species after oral administration	Published chemical critique against mouse differential-efficacy data	Speciation analysis in physiological fluids
78	contested	Whether lithium is an essential trace element for mammals	Old deprivation studies and ecological correlations against no RDA, no deficiency syndrome and no lithium-dependent protein	Identification of a lithium-dependent protein

SOURCES AND METHOD

Bibliographic data for every reference in this volume were retrieved from **PubMed**, and each PubMed identifier was individually verified against PubMed metadata for journal, year and title before citation; digital object identifiers are given in the reference list. The full text of Aron and colleagues was read from PubMed Central (PMC12443616), with figure legends taken from the Europe PMC JATS XML of the same article, which is the source of the group sizes quoted in Chapter I.

Where a number exists only in a figure panel, a supplementary table or a deposited source-data file rather than in the text, methods or legends of a paper, this volume says so and does not quote it. That applies specifically to the MCI and AD group mean lithium concentrations, the percentage reduction in human disease, the human plaque-to-parenchyma ratio, and the lithium–amyloid binding constants. Unit conversions from nanograms per gram to molar are the author's arithmetic, using an atomic mass of 6.941 and assuming one gram of tissue approximates one millilitre, and are flagged as such at first use.

Three claims of absence in this volume rest on exhaustive searches rather than on positive evidence, and are stated as absences: that no independent replication of the human measurement is indexed; that the intersection of reelin and lithium contains five records and no mechanistic study; and that lithium has never been tested against locus coeruleus degeneration. Searches were run to 15 September 2026 and should be repeated before any submission, since correspondence and matters-arising can lag indexing.

One retracted publication circulates widely in the secondary lithium and protein phosphatase 2A literature and is **not** cited here. Readers building on this chapter should check their own sources against it.

This volume makes no clinical recommendation. Its therapeutic chapters exist to establish what is not known.

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